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JÉSSICA ARAÚJO FIGUEIRA

Sex, pain, alcoholism and anxiety symptoms are predictive for systemic cortisol levels in oral cancer patients

Araçatuba – SP
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Tese apresentada à Faculdade de Odontologia de Araçatuba, Universidade Estadual Paulista "Júlio de Mesquita Filho''- UNESP, como parte dos requisitos para obtenção do título de ''Doutora em Odontologia''- Área de Concentração Estomatologia.

Orientador: Prof. Dr. Daniel Galera Bernabé
Coorientadora: Prof. Dra. Flávia Lombardi Lopes

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FIGUEIRA, J. A. **Sexo, dor, etilismo e sintomas de ansiedade são preditivos para níveis sistêmicos de cortisol em paciente com câncer de boca.** 2021. 46 f. Tese (Doutorado) - Faculdade de Odontologia, Universidade Estadual Paulista, Araçatuba, 2021.

RESUMO

Pacientes com câncer podem apresentar uma desregulação do eixo hipotálamo-hipófise-adrenal (HPA) e secreção aumentada do hormônio cortisol. Níveis elevados de cortisol têm sido associados a pior prognóstico de diferentes tipos de câncer. Embora alterações psicológicas como ansiedade e depressão possam deflagrar uma secreção anormal de cortisol, pouco se sabe sobre a influência destas desordens emocionais na desregulação do eixo HPA em pacientes com câncer quando avaliadas em conjunto com variáveis demográficas, clinicopatológicas e biocomportamentais. Este estudo transversal avaliou os níveis plasmáticos de cortisol em 133 pacientes com carcinoma espinocelular (CEC) de boca e sua associação com variáveis demográficas, clínicopatológicas, biocomportamentais e psicológicas. Os níveis plasmáticos de cortisol foram mensurados por eletroquimioluminescência, e os níveis de ansiedade e depressão foram avaliados pelo Inventário de Ansiedade (BAI) e de Depressão (BDI) de Beck, respectivamente. Os dados demográficos, clinicopatológicos e biocomportamentais foram coletados dos prontuários dos pacientes. Os resultados da análise multivariada mostraram que homens com CEC de boca apresentaram 4,5 vezes mais chances de terem níveis elevados de cortisol plasmático do que as mulheres com a doença (OR=4,472; p=0,018). A presença de dor relacionada ao tumor primário também foi preditivo para maiores níveis de cortisol (OR=5,388; p=0,003). A ausência de histórico de consumo crônico de álcool foi um fator protetor para concentrações muito elevadas do hormônio nos pacientes com CEC de boca (OR=0,104; p= 0,004). Sintomas de ansiedade mensurados pelo BAI como “mãos trêmulas” (OR=0,192; p= 0,016) e estar “nervoso” (OR=0,207; p= 0,0004) foram associados a menores níveis de cortisol. Por outro lado, o sentimento de “medo de perder o controle” foi um fator de risco para níveis muito elevados de cortisol plasmático (OR=6,508; p= 0,0004). O score global e os sintomas específicos de depressão mensurados pelo BDI não foram preditivos para os níveis plasmáticos hormonais (p<0,05). Juntos, os resultados mostram que sexo, dor, consumo de álcool e sintomas de ansiedade são variáveis independentes para os níveis sistêmicos de cortisol nos pacientes com câncer de boca. Portanto, intervenção psicológica, bem

como o controle da dor e do alcoolismo devem ser considerados para a prevenção dos efeitos negativos da desregulação da secreção de cortisol nos pacientes diagnosticados com câncer de boca.

Palavras-chave: Sistema hipotálamo-hipofisário. Glucocorticoides. Estresse psicológico. Ansiedade. Depressão. Neoplasias. Neoplasias de cabeça e pescoço. Neoplasias bucais.

FIGUEIRA, J. A. **Sex, pain, alcoholism and anxiety symptoms are predictive for systemic cortisol levels in oral cancer patients.** 2021. 46 f. Tese (Doutorado) - Faculdade de Odontologia, Universidade Estadual Paulista, Araçatuba, 2021.

ABSTRACT

Cancer patients may have a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and abnormal secretion of cortisol. Increased cortisol levels have been associated with worse prognosis in different types of cancer. Although anxiety and depression can trigger an abnormal cortisol secretion, little is known regarding the influence of these emotional disorders on HPA axis dysregulation in cancer patients when evaluating together with demographic, clinicopathological and biobehavioral variables. This cross-sectional study analyzed the plasma cortisol levels of 133 patients with oral squamous cell carcinoma (OSCC) and its association with demographic, clinicopathological, biobehavioral and psychological variables. Plasma cortisol levels were measured by electrochemiluminescence, and anxiety and depression symptoms were assessed using Beck Anxiety Inventory (BAI) and Depression (BDI), respectively. Demographic, clinicopathological and biobehavioral data were collected from patients' medical records. Results from multivariate analysis showed that men with OSCC were 4.5 times more likely to have higher plasma cortisol levels than women (OR = 4.472, p = 0.018). The presence of cancer-induced pain was predictive for higher cortisol levels (OR = 5.388, p = 0.003). The absence of chronic alcohol consumption history was a protective factor for highest hormonal concentrations in oral cancer patients (OR = 0.104, p = 0.004). Anxiety symptoms measured by BAI as "hands trembling" (OR = 0.192, p = 0.016) and being "nervous" (OR = 0.207, p = 0.0004) were associated with lower cortisol levels. In contrast, the feeling of “fear of losing control” was a risk factor for highest systemic levels cortisol (OR = 6.508, p = 0.0004). The global score and specific symptoms of depression measured by the BDI were not predictive for plasma hormone levels (p <0.05). Together, our results show that sex, pain, alcohol consumption and anxiety symptoms are independent variables for systemic cortisol levels in patients with oral cancer. Therefore, psychological intervention, as well as control of pain and alcohol consumption, should be considered to prevent the negative effects of cortisol secretion dysregulation in patients with oral cancer.

Keywords: Hypothalamo-hypophyseal system. Glucocorticoids. Stress, psychological. Anxiety. Depression. Neoplasm. Head and neck neoplasms. Mouth neoplasm.

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SUMÁRIO

Sex, pain, alcoholism and anxiety symptoms are predictive for systemic cortisol levels in oral cancer patients

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1 INTRODUCTION*

Cancer onset and progression can be affected by psychoneuroimmunological factors (Mravec et al., 2006; Recio, 2019; Mravec et al., 2020). Stress, anxiety and depression result in neurohormonal dysregulation affecting the immune system and cancer progression (Spiegel and Giese-Davis, 2003; Reiche et al., 2004; Antoni et al., 2006; Thaker et al., 2007). The neuroendocrine and immune systems share common mediators and receptors signals, suggesting that the brain plays an immunoregulatory role (Ader et al., 1995). Psychological processes activate the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis, promoting increased secretion of stress-related neurohormonal mediators, such as catecholamines and cortisol (Shin et al., 2016). It has been shown that cortisol plays a role in tumorigenesis and cancer progression (Antoni et al., 2006; Bernabé et al., 2011; Xie et al., 2015; Zhang et al., 2020). The hormone may promote DNA damage and interfere on DNA repair, an event eminently mediated by glucocorticoid receptors (Flint et al., 2007; Jenkins et al., 2014). In a pre-clinical model of chronic stress, Feng et al. observed increased tumorigenesis and attenuation of p53 function which could be mediated by elevated glucocorticoids levels (Feng et al., 2012). Abnormal plasma cortisol levels have been associated with shorter disease-free interval in ovarian and breast cancer (Schrepf et al., 2015, Zeitzer et al., 2016). In addition, a stimulatory effect of cortisol on cell proliferation has been observed in different cancer cell lines (Simon et al., 1984; Zhao et al., 2000; Bernabé et al., 2011).

Neuroimmunological alterations resulting from cancer-induced HPA axis dysregulation, may be involved in the etiopathogenesis of physical and psychological disorders in cancer patients, through activation of pro-inflammatory cytokines in the

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hypothalamus (Kim et al., 2016; Schmidt et al., 2016; Figenschau et al., 2018). In general, cancer patients experience high levels of stress, anxiety and depression during different phases of cancer diagnosis and treatment (Cordes et al., 2014; Majid et al., 2017). Association between cortisol levels and psychological symptoms has been demonstrated in healthy and oncological patients (Aarstad et al., 2005; Sharma et al., 2018; Jia et al., 2019). In a recent study, high systemic cortisol levels were associated with depression and occurrence of anxiety symptoms in healthy patients (Jia et al., 2019). Newly diagnosed lung cancer patients, for example, display higher levels of depression as well as higher salivary cortisol levels (Chang and Lin, 2017).

Head and neck cancer (HNC) comprises malignancies of the upper aero digestive tract as oral cavity, oropharynx, pharynx and larynx, and is the seventh most common type of cancer in the world (Bray et al., 2018). Among HNCs, oral squamous cell carcinomas (OSCC) are the most frequent, with chronic tobacco and alcohol consumption being the main risk factors (Chi et al., 2015). Despite advances in cancer diagnosis and treatment, the 5-year survival rate is only 50% for patients with OSCC (Kumar et al., 2016). In a previous study, we showed that patients with OSCC have higher systemic cortisol levels compared to health volunteers or patients with oral potential malignant disorder (OPMD) (Bernabé et al., 2012). In addition, increased cortisol levels were associated with advanced stage of oral cancer (Bernabé et al., 2012). Patients with HNC, including OSCC, also experience emotional disorders such as depression and anxiety (Cohen et al., 2016). Increased anxiety and depression levels in HNC patients have been associated with regional lymph node metastases, shorter survival and worse quality of life (Aarstad et al., 2005; Shiraz et al., 2014; Dunne et al., 2017; Rieke et al., 2017).

Despite the evidence of emotional disorders and dysregulation of cortisol secretion, no study has focused on the interaction of these phenomena in HNC patients. Furthermore, little is known regarding the independent predictors for HPA axis dysregulation in patients with cancer, when clinicopathological, biobehavioral and psychological variables are analyzed together. Although dysregulation of HPA axis has been reported in cancer patients, the joint role of clinical and psychological predictors remains unclear. In the current study we analyzed for the first time the association of plasma cortisol levels with clinicopathological, biobehavioral and psychological variables in patients with oral cancer.

2 PATIENTS AND METHODS

2.1 Ethics statement

This study was approved by the Committee of Human Studies of the Sao Paulo State University (UNESP), School of Dentistry, Araçatuba, SP-Brazil (nº. 35314720.9.0000.5420) and informed consent was obtained from all participants.

2.2 Patients

The patients with oral cancer were recruited from the Oral Oncology Center, Sao Paulo State University (UNESP), School of Dentistry, Araçatuba, São Paulo, Brazil. Inclusion criteria were patients over 18 years of age; with histopathological diagnosis of OSCC; and primary tumor located in anterior two-thirds of the tongue, floor of the mouth, retromolar area, buccal mucosa, gingiva or hard palate. Exclusion criteria were previous history of cancer; any previous oncological treatment; or inability to perform blood collection or psychological tests.

2.3 Clinicopathological variables

Clinical e histopathological data were collected from patients' clinical records. Demographic variables (age, sex, marital status, living with someone, education and family income), clinicopathological variables (comorbidity, pain related to the primary tumor, clinical staging, primary tumor size (T), presence of regional metastases (N) and tumor histological grade) and biobehavioral data (sleep quality, history and intensity of tobacco and alcohol consumption) were obtained in OSCC patients' admission. Comorbidities were assessed according to the Charlson Comorbidity Index (CCI) (Charlson et al., 1987). Clinical staging was defined according to the Union for International Cancer Control (UICC) (Sobin et al., 2009). Visual Analog Scale were used to estimate de intensity of pain at the tumor site, classified in a scale from 0

(absence of pain) to 10 (severe pain). The patient's sleep quality in the previous night was classified as very good, good, regular, bad and terrible. Tobacco and alcohol consumption intensity was assessed using a score scale of 1 to 4 points according to the amount of cigarette or doses of alcohol per day (Sarafim-Silva et al., 2018).

2.4 Anxiety and depression symptoms

Anxiety and depression symptoms were assessed by interviews using the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI), respectively (Beck et al., 1988; Beck et al., 1993; Sarafim-Silva et al., 2018; Bastos et al., 2018). The tests were applied by a psychologist on the same day of blood samples collection. BAI and BDI are a self- report inventory with 21 items which evaluate the frequency of anxiety and depression symptoms that occurred in the last week (Beck et al., 1988; Beck et al., 1993). In both scales, the severity of each anxiety or depression symptoms ranged from 0 (absolutely not) to 3 (frequently). The overall BAI and BDI scores were graded with 4 levels, ranging from minimal to severe level.

2.5 Blood samples

Blood samples were collected from oral cancer patients before oncological treatment and on the same day as the psychological evaluation. Blood collection were performed between 8:00 am and 10:00 am to avoid diurnal variations. In order to prevent clotting, samples of peripheral blood were collected with a syringe treated with EDTA. After collection, samples are immediately centrifuged at 1500 rpm under refrigeration at 4ºC for 20 minutes and plasma was stored at -80ºC.

2.6 Measurement of plasma cortisol

Plasma cortisol levels were measured by electrochemiluminescence immune assay method using the Elecsys Cortisol II reagent kit (Roche Diagnostics GmbH,

Mannheim, Germany) in a Cobas E411 auto analyzer (Roche Diagnostics GmbH, Mannheim, Germany). This assay is based on the competition test principle, using a specific monoclonal antibody against cortisol and a ruthenium-labeled analogue (Fung et al., 2017). The chemiluminescent reaction was induced by applying a voltage to the electrode and measured by a photomultiplier (Fung et al., 2017). The assay was performed according to the manufacturer's instructions. The detection limit of the assay was 1.5 nmol/L and measuring range was 1.5 to 1750 nmol/L.

2.7 Statistical analysis

Statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Inc, Cary, North Carolina). Chi-square and Fisher's exact tests were used to evaluate the association between cortisol plasma levels and demographic, clinicopathological or biobehavioral variables, as well as the anxiety and depression symptoms of the OSCC patients. Multivariate regression analysis was performed by the stepwise logistic regression method, considering the plasma cortisol levels as a dependent variable, and the demographic, clinicopathological, biobehavioral and psychological characteristics as explanatory variables. Logistic regression was performed considering two different models according to the categorization of plasma cortisol levels. In model 1 scores below and above the median were used to define patients with lower and higher plasma cortisol levels, respectively. In model 2 cortisol concentrations were categorized by quartile in very high, high, low and very low plasma cortisol levels. The median was also used as cutoff point for BAI and BDI scores. Each anxiety and depression symptom reported in BAI and BDI, respectively, was also analyzed separately by two different measures: binary measure according to symptom occurrence (yes or no) and severity categories (none, mild, moderate, or intense). Significance level was set at 5% ($p<0.05$) for all analyses.

3 RESULTS

3.1 Epidemiological and clinicopathological characteristics

One hundred and thirty-three patients with OSCC met the inclusion criteria. Their demographic and clinicopathological characteristics are showed in Table 1. Most of the patients were man (78.8%), middle aged (63.2%) and married (51.1.%). The minority lived alone (12.4%), whereas 87.6% live with a partner or relative. Most patients had completed elementary school (48.2%), and family income of R$1000-5000 (1 USD = 5 Reais, approximately) per month (45.7%). Regarding clinicopathological data, tongue (39.8%) and floor of the mouth (27.1%) were the most common sites of OSCC. The majority of patients had the disease classified in stage IV (38.3%), and tumors microscopically graded in moderately differentiated (66.0%). Forty-three percent of the OSCC patients reported pain related to the primary tumor. Most of the patients had moderate pain (23.7%), followed by 12.4% with minimum pain and 7.2% with intense pain. Sixty-one patients displayed at least one comorbidity (45.9%) (Table 1).

Table 1. Demographic and clinicopathological characteristics of OSCC patients

Variable	Nº (%)
Sex	
Male	105 (78.9)
Female	28 (21.1)
Age	
0-45 y	18 (13.5)
46-65 y	84 (63.2)
>65 y	31 (23.3)
Marital status	
Single	31 (23.3)
Married	68 (51.1)
Divorced	18 (13.5)
Widowed	16 (12.0)
Living alone*	
No	71 (87.6)
Yes	10 (12.4)
Education*	
Illiterate	4 (4.9)
Incomplete primary school	19 (23.5)
Elementary school	39 (48.2)
High school	15 (18.5)
University	4 (4.9)
Income*	
R$0/mo	5 (6.1)
<R$1000/mo	23 (28.4)
R$1000-5000/mo	37 (45.7)
>R$5000/mo	16 (19.8)
T classification	
T1	32 (24.1)
T2	35 (26.3)
T3	28 (21.1)
T4	38 (28.6)
Regional metastasis	
N0	93 (69.9)
N+	40 (30.1)
Clinical stage	
I	32 (24.1)
II	32 (24.1)
III	18 (13.5)
IV	51 (38.3)
Histopathologic grade*	
In situ	5 (4.7)
Well-differentiated	25 (23.6)
Moderately-differentiates	70 (66.0)
Poorly-differentiated	6 (5.7)
Comorbidity	
No	72 (54.1)
Yes	61 (45.9)
CCI score	
0	72 (54.1)
1	43 (32.3)
2	14 (10.5)
3	4 (3.0)
Pain intensity*	
No	55 (56.7)
Minimum	12 (12.4)
Moderate	23 (23.7)
Intense	7 (7.2)

Abbreviation: CCI, Charlson Comorbidity Index
*Variables with missing data

3.2 Biobehavioral and psychological characteristics

The biobehavioral and psychological variables of OSCC patients are described in Table 2. Most patients were smokers (73.7%). In relation to tobacco consumption intensity, 29.3% of the patients reported light, 30.1% moderate and 26.3% heavy tobacco consumption. The majority of patients were drinkers (55.6%) and most of them had a history of a heavy alcohol intake (36.8%). More than half of the patients reported good quality of sleep in the previous night (50.5%), while 17.5% classified the sleep in very good, 23.8% in regular and 4.1% reported have had a bad or terrible sleep. Regarding psychological characteristics, most of OSCC patients displayed the minimum level of anxiety (68.8%) and depression (67.9%) symptoms, followed by mild (20.4%, BAI; 21.4%, BDI), moderate (8.6%, BAI; 9.5%, BDI) and severe (2.1%, BAI; 1.2%, BDI) (Table 2).

Table 2. Biobehavioral and psychological characteristics of OSCC patients

Variable	Nº (%)
Smoking	
Non-smoker	19 (14.3)
Current smoker	98 (73.7)
Ex-smoker	16 (12.0)
Tobacco intensity	
Non-smoker	19 (14.3)
Light	39 (29.3)
Moderate	40 (30.1)
Heavy	35 (26.3)
Alcohol consumption	
Non-drinker	25 (18.8)
Current drinker	74 (55.6)
Ex-drinker	34 (25,6)
Alcohol intensity	
Non-drinker	25 (18.8)
Light	36 (27.1)
Moderate	23 (17.3)
Heavy	49 (36.8)
Sleep quality (previous night)*	
Very good	17 (17.5)
Good	49 (50.5)
Regular	23 (23.8)
Bad	4 (4.1)
Terrible	4 (4.1)
BAI*	
Minimum	64 (68.8)
Mild	19 (20.4)
Moderate	8 (8.6)
Severe	2 (2.1)
BDI*	
Minimum	57 (67.9)
Mild	18 (21.4)
Moderate	8 (9.5)
Severe	4 (1.2)

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory.
*Variables with missing data

3.3 Associations between plasma cortisol levels and demographic, clinicopathological, biobehavioral and psychological variables

Univariate analysis considering cortisol concentrations stratified into two levels showed that male patients displayed higher levels of plasma cortisol compared to females (p=0.005) (Table 3). When the associations between clinicopathological variables and cortisol levels were analyzed, OSCC patients who developed regional metastasis showed increased cortisol levels than patients without regional metastasis (p=0.030). The presence and intensity of pain related to primary tumor were associated with higher plasma cortisol levels. OSCC patients who had pain, regardless of intensity, showed higher levels of plasma cortisol than patients without pain (p=0.003). Also, patients that had intense pain displayed higher plasma cortisol levels in comparison to patients with moderate and minimum intensity or no pain (p=0.015). Regarding the biobehavioral variables, both alcohol consumption and intensity were positively associated with hormonal levels. Drinker OSSC patients had higher levels of plasma cortisol than non-drinker or ex-drinker patients (p=0.005), and higher alcohol consumption was also associated with increased hormonal levels (p=0.015). In univariate analysis, global anxiety scores were not associated to plasma cortisol levels. However, significant associations were observed between hormonal levels and specific anxiety symptoms measured by BAI. Cancer patients who reported occurrence of “dizzy or lightheaded” (p=0.038), “heart pounding/racing” (p=0.02) and “hands trembling” (p=0.03) had lower levels of plasma cortisol compared to patients without these symptoms. Severe intensity of the symptoms “heart pounding/racing” (p=0.03) and of being “scared” (p=0.04) were also associated to lower plasma cortisol levels (Table 3). When quartile categorization was used to stratify cortisol concentrations, highest cortisol levels were associated with male sex, mid education (elementary school), smoking, alcoholism and pain related to the tumor. Regarding psychological

factors, highest levels of cortisol were also associated to the anxiety symptom “fear of losing control”, the depression symptom “suicide ideation” and the presence of one or more depression symptoms (Table 3).

Table 3. Significant associations between demographic, clinicopathological, behavioral and psychological variables and plasma cortisol levels on patients with OSCC from the univariate analysis

Variable[a]	**Median (*P-value*)**	**Quartile (*P-value*)**
Sex (male)	.004	.047
Education (elementary school)	-	.031
Regional metastasis (N)	.030[b]	-
Pain	.002[b]	.022[b]
Pain intensity (intense)	.015[c]	-
Smoking	-	.018[d]
Alcohol consumption (current drinker)	.005[d]	.025[d]
Alcohol intensity (heavy intensity)	.015[e]	-
Anxiety symptoms (BAI)		
“dizzy or lightheaded”	.038[b]	-
“heart pounding/racing”	.018[b]	-
“heart pounding/racing” intensity	.033[c]	-
“hands trembling”	.026[b]	-
“scared”	.046[f]	-
“fear of losing control”	-	.022[b]
Depression symptoms (BDI)		
Depression symptom (yes vs no)	-	.000[b]
“suicide ideation”	-	.047[b]

[a]The variables' associations with plasma cortisol levels reached statistical significance.
[b]Values were measured with the binary measure (yes or no).
[c]Values were measured with the severity categories (none, mild, moderate, or intense).
[d]Non- smoker/drinker, current smoker/drinker, or ex-smoker/drinker.
[e]Light, moderate, or heavy.
[f]Little (none and mild), or very (moderate and intense).

3.4 Predictive value of demographic, clinicopathological, biobehavioral and psychological variables for plasma cortisol levels

To identify which variables are predictive of diurnal cortisol secretion in oral cancer patients, logistic regression analyses were performed considering cortisol concentrations stratified into two levels (model 1) and quartiles (model 2). Multivariate analysis using model 1 showed that male OSCC patients were 4.5 times more likely to display high plasma cortisol levels (OR=4.472, 95% CI=1.282 – 15.596, p=0.018) (Table 4). OSCC patients who reported pain related to primary tumor displayed 5.3 times more chances of have increased levels of plasma cortisol (OR=5.388, 95% CI=1.75 – 16.587, p=0.003). Moreover, one anxiety symptom was considered a protection factor to increased cortisol levels in patients with oral cancer. Patients who self- reported “hands trembling” in BAI evaluation had 81% less chance of having increased hormonal levels than patients who did not have the symptom (OR=0.192, 95% CI=0.05 – 0.741, p= 0.016) (Table 4). When cortisol concentrations were stratified in quartiles (model 2) the occurrence of pain related to tumor remained as a risk factor for the highest levels of cortisol in OSCC patients (OR=2.634, 95% CI=1.135 – 6.113, p=0.024) (Table 4). Using model 2 in logistic regression, alcohol abstinence was a protection factor against elevated cortisol levels. OSCC patients who were non-drinkers had 90% less chance of displaying very high cortisol levels than drinkers (OR=0.104, 95% CI=0.03 – 0.353, p= 0.004). Regarding psychological evaluation, two anxiety symptoms were predictive for cortisol levels in the multivariate analysis using model 2. OSCC patients who reported being nervous had 80% lower chances of developing very high plasma cortisol levels (OR=0.207, 95% CI=0.087 – 0.497, p= 0.0004). In contrast, the symptom “fear of losing control” was considered a risk factor for the highest concentrations of cortisol. OSCC patients who reported being afraid of

losing control had a 6.5-fold increase in the chance of displaying very highplasma cortisol levels (OR=6.508, 95% CI=2.328 – 18.194, p= 0.0004) (Table 4). Our results showed that both global depression levels, as well as specific depression symptoms, were not predictive to plasma cortisol levels in OSCC patients, regardless of the logistic regression model used.

Table 4. Significant results from stepwise logistic regression analyses considering plasma cortisol levels as response variable and demographic, clinicopathological, behavioral and psychological data as independent variables in OSCC patients.

	Independent Variable: Plasma Cortisol Levels					
	Model 1[a]			Model 2[b]		
Dependent Variables	OR	95% CI	*P*	OR	95% CI	*P*
Sex (male vs female)	4.472	1.282 – 15.596	0.018	-	-	-
Pain[c]	5.388	1.75 – 16.587	0.003	2.639	1.135 – 6.113	0.024
Alcohol consumption (non-drinker vs drinker)[c]	-	-	-	0.104	0.03 – 0.353	0.004
Anxiety symptoms (BAI)						
"hands trembling"[c]	0.192	0.05 – 0.741	0.016	-	-	-
"nervous"[c]	-	-	-	0.207	0.087 – 0.497	0.0004
"fear of losing control"[c]	-	-	-	6.508	2.328 – 18.194	0.0004

[a]Considering model 1 (cortisol levels categorized into two categories).
[b]Considering model 2 (cortisol levels categorized into four categories).
[c]Values were measured with the binary measure (yes or no).

4 DISCUSSION

In the last few decades, there has been a growing body of evidence showing the role of cortisol dysregulation in immune system impairment and cancer progression. In the current study, we investigated the predictive factors for systemic cortisol levels in oral cancer patients exploring demographic, clinicopathological, biobehavioral and psychological variables. The results revealed that sex, pain, alcohol consumption and anxiety symptoms are independent variables for diurnal cortisol levels in cancer patients. Multivariate analysis showed that the male sex and presence of pain related to the primary tumor were independently associated with increased plasma cortisol levels. Male OSCC had 4.4 times more chances to display increased plasma cortisol levels, when compared to female patients. In a previous study, we found that salivary levels of cortisol but not plasma levels, were higher in men than women with oral cancer (Bernabé et al., 2012). Comparing to our previous study, in the current study we used a larger number of OSCC patients which may have contributed to the identification of a significant association between sex and plasma hormonal levels. There is a variability of results in the literature regarding differences in cortisol secretion between men and women, both under normal (Seeman et al., 2001; Larsson et al., 2009; Gunn et al., 2016) and stressful situations (Kudielka et al., 1998; Kotlyar et al., 2017; Helbig and Backhaus, 2017). While some studies show that women (Gunn et al., 2016; Larsson et al., 2009) or men (Seeman et al., 2001) exhibit increased systemic levels of cortisol, other studies were unable to demonstrate significant differences between the sexes (Kotlyar et al., 2017; Helbig and Backhaus, 2017). Nevertheless, this seems to be the first study that shows that men with cancer have an elevated diurnal cortisol secretion than women with the same type of tumor. Kudielka et al. observed increased salivary free cortisol responses to stress in healthy elderly

men compared to elderly woman, although there were no differences in plasma cortisol responses to stress between sexes in all age groups, (Kudielka et al., 2004). Most of the sample in the current study were of middle aged and elderly male patients who are experiencing an extremely stressful situation after cancer diagnosis, what may be contributing to the differences in cortisol levels cortisol levels found between sexes.

Our results showed that oral cancer patients with pain had a 5.3-fold increase in the chance of having high plasma cortisol levels. Hyperactivation of HPA axis induced by stress and subsequently cortisol disfunction are linked to pain and inflammation (Edwards et al., 2008; Tak and Rosmalen, 2010; Quartana et al., 2010). Anxiety has also been identified as a significant predictor of pain (Pincus et al., 2002; Bair et al., 2013). Pain itself can be a stressor, and maladaptive response to pain may intensify the symptom (Thornton et al., 2010). In patients with advanced cancer, Dev et al. (2011) observed a significant association between elevated serum cortisol levels and increased pain (Dev er al., 2011). Our results demonstrated not only the association of elevated tumor-induced pain and cortisol secretion, but also the presence of pain as an independent variable for increased systemic cortisol levels. These findings indicate the importance of an effective pain control in cancer not only for a better patient's quality of life, but also to prevent detrimental effects of neurohormonal dysregulation.

Univariate analysis showed that alcohol consumption by cancer patients was associated with increased systemic cortisol levels. Moreover, in the multiple regression using model 2, abstaining from alcohol was a protect factor for highest cortisol levels in OSCC patients. The relationship between alcohol consumption and HPA axis dysfunction seems to be a two-way street. Evidence suggests that alcohol can directly stimulates HPA axis and glucocorticoid receptors in brain regions (extrahypothalamic,

limbic forebrain, and medial prefrontal cortex circuits) contributing to onset and progression of alcohol use disorder (Blaine and Sinha, 2017). Cortisol in turn may influence the cognitive process and promote habit-based learning, which can contribute to habit formation and relapses (Stephens and Wand, 2012). Both HPA axis dysfunction and exposure to stress interact and became a critical component for developing alcohol use disorders (Schepis et al., 2012). In rodents, heavy alcohol consumption leads to increased levels of cortisol, in addition to changes in HPA axis feedback mechanism (Ogilvie et al., 1998). There is still a lack of studies investigating the mechanisms involved in systemic cortisol variation related to alcohol consumption in oncological patients. Our findings also showed that increased cortisol levels were linked with occurrence of regional metastasis in OSCC patients. In our previous investigation, albeit with a smaller sample group, we also observed that advanced-stage OSCC patients displayed increased plasma levels compared to early-stage patients. Although the association between regional metastasis e high cortisol levels has not been maintained in the logistic regression in the current study, it can indicate an association between dysregulation of the HPA axis and oral cancer progression. Rodents with OSCC treated with hydrocortisone had increased number of lymph-node and visceral metastases (Kage et al., 1988). In addition, *in vitro* studies have shown that glucocorticoids can increase cancer cell proliferation and tumor progression (Zhao et al., 2000; Bernabé et al., 2011; Buoso et al., 2019).

Persistent activation of the HPA axis due to prolonged exposure to stressful events (chronic stress) results in increased cortisol levels (Faravelli et al., 2012). HPA axis activity and abnormal cortisol secretion have been linked to the onset and maintenance of psychological disorders, such as anxiety and depression (Faravelli et al., 2012; Herbert, 2013; Pulopulos et al., 2020). Increased cortisol levels are associated with depression and anxiety symptoms in healthy and oncological patients

(Aarstad et al., 2005; Chang and Lin, 2017; Sharma et al., 2018; Jia et al., 2019). Sharma et al. explored the cortisol levels and psychological symptoms in OSCC patients (Sharma et al., 2018). The authors observed higher cortisol levels and higher anxiety and depression scores in the oncological patients compared to those with OPMD and health patients (Sharma et al., 2018). In their study, a small sample of patients were studied, and no association or regression analysis were applied to identify the interaction between hormonal and psychological data. Other studies evaluated cortisol and anxiety levels in HNC/OSCC patients, separately. Aarstad et al. observed higher anxiety and lower depression levels in HNC patients, when compares to patients with benign HN disease (Aarstad et al., 2005). Previously, we found increased levels of plasmatic and salivary cortisol in OSCC patients compared to healthy volunteers, smokers and drinkers and patients with OPMD (Bernabé et al., 2012). In the current study, global anxiety and depression scores were not predictive for cortisol levels in oral cancer patients. However, we observed that some specific anxiety symptoms were associated with systemic cortisol levels. OSCC patients who reported “fear of losing control” in BAI had 6.5 times more likely to displaying highest plasma cortisol levels. Cancer diagnosis and fear of treatment are highly stressful and potentially traumatic for the patients (Cordova et al., 2017). Our results suggest that the feeling of losing control triggered after diagnosis of a malignant disease and before treatment could incite diurnal secretion of aberrant cortisol levels. Conversely, BAI symptoms of “hands trembling” and being “nervous” were protector factors for increased cortisol levels in OSCC patients. The activation of the SNS is the main reason for the physical symptoms of anxiety disorders (Kaplan and Sadock, 1998). It is worth considering that the physical symptoms triggered by anxiety are most likely influenced by catecholamines through SNS activity than by HPA response. An inverse correlation between anxiety and salivary cortisol levels was found in one study with

prostate cancer patients (Sharpley et al., 2017).

In view of the variability of results inherent to different anxiety symptoms, we hypothesize that there may be a discrepancy between what patients report in BAI and their true mental and emotional state that is really interfering with physiological stress levels such as cortisol secretion. Furthermore, patients may have difficulties to process the psychological alterations they are experiencing, affecting the consciousness of their anxiety status. In the logistic regression, depression symptoms measured by BDI were not predictors for cortisol levels in oral cancer patients. Our results showed that "suicide ideation" was associated with highest levels of cortisol in OSCC patients, however this depression symptom was not an independent predictor for hormonal levels. A positive correlation between cortisol levels and depression scores has been identified in healthy people (Jia et al., 2019). Elevated cortisol concentrations were also observed in depressed patients with advanced metastatic cancer (Jehn et al., 2006). Moreover, higher evening cortisol levels were associated with depression in ovarian cancer patients (Lutgendorf et al., 2008). The lack of association between depression and cortisol levels observed in the current study may be associated with the exceptionally low percentage of OSSC patients classified with moderated and severe depression.

This study has some limitations. Cortisol concentrations were analyzed in plasma samples collected once daily (in the morning), so the circadian rhythm of OSCC patients was not analyzed. Also, hormonal measurement was only performed in the pre-treatment period, making it impossible to know the cortisol secretion profile during and after cancer treatment, or the variables which could influence hormonal levels in these periods. In addition, we were not able to demonstrate whether cortisol levels have impact on OSCC patient's prognostic. Further studies with these oral cancer

patients in an appropriate follow- up cut may reveal whether cortisol levels or HPA axis dysregulation affect the global and disease-specific survival. In conclusion, our results reveal that male sex, pain, alcoholism, and the feeling of fear of losing control are associated with increased systemic cortisol levels in OSCC patients. Moreover, this is the first evidence that specific anxiety symptoms can act as protective or risk factors to plasma cortisol levels in cancer patients. Psychological intervention, as well as strict pain control and drinking habits management should be considered in the treatment approach of oncological patients. These strategies could lead to greater well-being and prevent negative effects of diurnal cortisol dysregulation on cancer progression.

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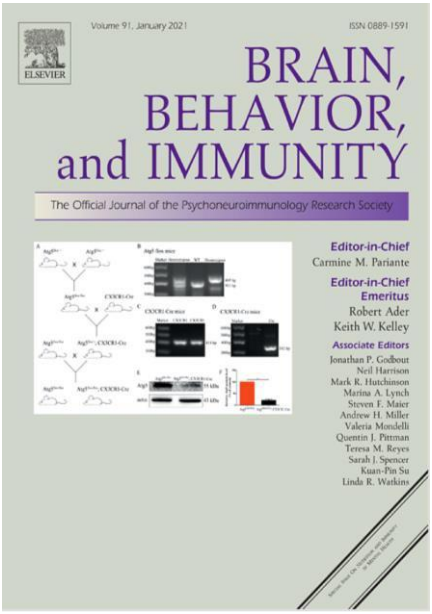
ANEXOS

ANEXO A – Periódico de interesse para submissão

Brain, Behavior, and Immunity



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ANEXO B – Parecer Comitê de Ética em Pesquisa

UNESP - FACULDADE DE ODONTOLOGIA-CAMPUS DE ARAÇATUBA/ UNIVERSIDADE ESTADUAL PAULISTA "JÚLIO DE MESQUITA FILHO"

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Análise da associação dos níveis de cortisol plasmático com sintomas de ansiedade e depressão em pacientes com câncer de boca e orofaringe

Pesquisador: JESSICA ARAUJO FIGUEIRA

Área Temática:

Versão: 2

CAAE: 35314720.9.0000.5420

Instituição Proponente: Universidade Estadual Paulista Júlio de Mesquita Filho

Patrocinador Principal: Universidade Estadual Paulista Júlio de Mesquita Filho

DADOS DO PARECER

Número do Parecer: 4.294.478

Apresentação do Projeto:

Pesquisas tem demonstrado que fatores psicológicos podem influenciar na incidência e progressão do câncer através de desregulação neurohormonal que afeta o sistema imune. Até o momento poucos estudos tem avaliado a associação de alterações psicológico-neuro-hormonais em paciente com câncer de cabeça e pescoço. Por este motivo, este estudo terá como objetivo analisar a associação dos níveis plasmáticos de cortisol com sintomas de ansiedade e depressão em pacientes com câncer de boca e orofaringe. Um total de 150 pacientes com câncer de boca (n=100) e orofaringe (n=50) serão incluídos no estudo. Serão utilizadas amostras de plasma já disponíveis no Banco de Tumor e dados comportamentais do Núcleo de Pesquisa em Psicossomática do Centro de Oncologia Bucal da FOA-UNESP. Os níveis de cortisol plasmático serão mensurados pelatécnica de eletroquimioluminescência. Para avaliar os níveis de sintomas psicológicos de ansiedade e depressão foi utilizado o Inventário de Ansiedade e Depressão de Beck. Testes estatísticos específicos serão utilizados para avaliar a associação dos níveis plasmáticos de cortisol com sintomas de ansiedade e depressão, bem como com as características clinico-patológicas e sociodemográficas de pacientes com câncer de boca e orofaringe.

Objetivo da Pesquisa:

Objetivo Primário:

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Bairro: VILA MENDONCA **CEP:** 16.015-050
UF: SP **Município:** ARACATUBA
Telefone: (18)3636-3200 **Fax:** (18)3636-3332 **E-mail:** andrebertoz@foa.unesp.br

Analisar a associação dos níveis plasmáticos de cortisol com sintomas de ansiedade e depressão em pacientes com câncer de boca e orofaringe.

Objetivo Secundário:

1 - Avaliar os níveis plasmáticos pré-tratamento de cortisol em pacientes com câncer de boca e orofaringe;

2 - Avaliar os sintomas de ansiedade em pacientes com câncer de boca e orofaringe;

3 - Avaliar os sintomas de depressão em pacientes com câncer de boca e orofaringe;

4 - Analisar a associação dos níveis plasmáticos de cortisol com as variáveis demográficas, clinicopatológicas e biocomportamentais de paciente
com câncer de boca e orofaringe;

5 - Analisar a correlação dos níveis plasmáticos de cortisol com sintomas de ansiedade e depressão.

Avaliação dos Riscos e Benefícios:

Riscos:

Este estudo oferece riscos mínimos aos seus participantes, pois suas metodologias são: coletas de sangue e saliva cujas técnicas são amplamente conhecidas e aplicadas em laboratórios de diagnóstico. Os testes psicológicos que serão utilizados são reconhecidos mundialmente e validados na população brasileira e estes serão aplicados por um profissional da área de psicologia.

Benefícios:

A aplicação dos questionários psicológicos serão realizadas por um profissional da área de psicologia que oferecerá suporte psicológico ao paciente caso aja necessidade. A pesquisa favorece o processo de percepção de fatores inconscientes que possam influenciar no modo de viver do indivíduo e de como estes fatores podem interferir na própria doença.

Comentários e Considerações sobre a Pesquisa:

A pesquisadora adequou o número de pacientes que integrarão a pesquisa (n=280) no projeto detalhado e no resumo do projeto contido na Brochura (Informações básicas do projeto). Foi adequado também que o início da pesquisa está prevista para outubro/2020.

Considerações sobre os Termos de apresentação obrigatória:

A pesquisadora solicitou dispensa do TCLE. Ela menciona que o material biológico e os dados psicológicos que serão utilizados na presente pesquisa foram coletados em projetos anteriores

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que já possuem TCLE e aprovação de comitê de ética (Números do pareceres: FOA-01314-2011 e 1.653.722).

Recomendações:

Não há.

Conclusões ou Pendências e Lista de Inadequações:

Recomendo a aprovação do projeto, visto que foram realizadas as adequações.

Considerações Finais a critério do CEP:

Salientamos que, de acordo com a Resolução 466 CNS, de 12/12/2012 (título X, seção X.1., art. 3, item b, e, título XI, seção XI.2., item d), há necessidade de apresentação de relatórios semestrais, devendo o primeiro relatório ser enviado até 01/03/2021.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1570185.pdf	26/08/2020 09:44:59		Aceito
Projeto Detalhado / Brochura Investigador	ProjetodePesquisa.pdf	26/08/2020 09:41:03	JESSICA ARAUJO FIGUEIRA	Aceito
Outros	ParecerCEP1653722.pdf	10/07/2020 09:25:26	JESSICA ARAUJO FIGUEIRA	Aceito
Outros	ParecerCEPFOA013142011.pdf	10/07/2020 09:24:49	JESSICA ARAUJO FIGUEIRA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	SolicitacaodeDispensadoTCLE.pdf	10/07/2020 09:23:39	JESSICA ARAUJO FIGUEIRA	Aceito
Folha de Rosto	FolhadeRosto.pdf	10/07/2020 09:22:13	JESSICA ARAUJO FIGUEIRA	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

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Continuação do Parecer: 4.294.478

ARACATUBA, 23 de Setembro de 2020

Assinado por:
Aldiéris Alves Pesqueira
(Coordenador(a))

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