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Association between gender, estrogen receptors genes and anxiety levels in patients undergoing orthognathic surgery

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ABSTRACT

Orthognathic surgery is a procedure that is performed for the correction of dentofacial deformities and can lead to a change in an individual's anxiety levels. Anxiety is a multifactorial condition in which hormones and genes play an important role. This study aimed to evaluate if gender and genetic polymorphisms in estrogen receptor alpha (*ESR1*) and beta (*ESR2*) are associated with anxiety levels in patients undergoing orthognathic surgery. In this longitudinal observational study, 44 patients were included. Anxiety level assessments were performed at three time periods: 2 days before the surgical procedure and 1 and 6 months postoperatively, using the State-Trait Anxiety Inventory Scale. Gender, age, and facial profile were also evaluated. Additionally, a saliva sample from each individual was collected for the genotypic evaluation of ESR1 (rs2234693 and rs9340799) and ESR2 (rs1256049 and rs4986938) using real time polymerase chain reaction. Data were analyzed with a significance level of 0.05. There was a decrease in trait-anxiety and state-anxiety when comparing the preoperative measurements with those obtained 1 and 6 months postoperatively ($p < 0.05$). Females were more anxious than males at each time point during the study ($p < 0.05$). The genetic polymorphism rs9340799 in *ESR1* was associated with state-anxiety during the preoperative period ($p = 0.046$). In conclusion, an individual's gender and genetic polymorphism in *ESR1* are associated with anxiety in orthognathic surgery patients.

1. Introduction

Anxiety is an emotion characterized by feelings of tension, worried thoughts, and physical changes (Kazdim, 2000). Trait-anxiety is stable differences of propensity in the way an individual usually reacts to disturbing situations in their daily life, and state-anxiety is a momentary and transient emotional condition (Lai et al., 2002). There are several anxiety measurement tools in the literature. The State-Trait Anxiety Inventory (STAI) is the most used (Székely et al., 2007) and consists of a questionnaire that evaluates the traits and state of anxiety (Fioravanti et al., 2006).

Many studies have demonstrated that women have consistently higher prevalence rates of anxiety disorders than men (Altemus et al., 2014; Bruce et al., 2005; Comings et al., 1999; McLean et al., 2011). Changes in the levels of circulating estrogen have been associated with changes in the prevalence of anxiety (Patton et al., 1996; Ojeda and Bilger, 2000; Rocca et al., 2008; Yonkers, O'Brien and Eriksson, 2008). There is evidence in the literature that estrogen receptors (ERs) play a role in anxiety disorders (Comings et al., 1999; Ryan et al., 2011). The ERα and ERβ are highly homologous in structure and belong to one subclass of a large superfamily of nuclear hormone receptors (Burris et al., 2013). The ERα protein is coded by the *ESR1* gene, while ERβ is coded by the *ESR2* gene

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(Hapangama et al., 2015). Interestingly, genetic polymorphisms in *ESR1* and *ESR2* have been related to anxiety in humans (Comings et al., 1999; Ryan et al., 2011; Wang et al., 2013; Feng et al., 2017).

Approximately 20% of the world's population has some type of facial deformity (Sadek and Salem, 2007), which directly affects the quality of life and social satisfaction of these individuals (Westermark et al., 2001). Orthognathic surgery is an elective procedure that corrects severe dentofacial deformities in adults. Anxiety can directly affect the results of orthognathic surgeries due to a fear of death during the procedure, the anticipation of pain that may occur postoperatively, fear of physical incapacity, and concern related to the future facial appearance (Veronez and Tavano, 2005).

Anxiety problems are multifactorial, determined by the interaction of genetic and environmental factors (Gross and Hen, 2004). Therefore, this study aimed to evaluate if an individual's gender and genetic polymorphism in *ESR1* and *ESR2* are associated with anxiety levels in patients who are undergoing orthognathic surgery.

2. Materials and methods

2.1. Study design

This study was approved by the Research Ethics Committee of the Division of Health Sciences at the Federal University of Paraná (CAAE n° 58781916.4.0000.0102). This research followed the protocols of the Helsinki Declaration. This was a longitudinal observational study performed on 44 individuals who underwent orthognathic surgery at the Oral and Maxillofacial Surgery Service at the Hospital do Trabalhador in Curitiba, Brazil during March 2016 to December 2017. The sample was composed of individuals of both genders who were at least 18 years old, with indication for orthognathic surgery. All those who presented with some type of alteration and/or neurological impairment or alteration and/or genetic disease, or who underwent previous surgical procedures, such as orthognathic surgery and/or temporomandibular joint surgery, were excluded from the study.

The Brazilian population is ethnically heterogeneous because of the country size and immigration, there are several different ethnic groups living in the country. Curitiba is a large city in the south Brazil and is composed by 81.5% European descendant, 9.3% African descendant and mixed of Europeans and Africans descendants, and 9.2% Amerindian (Godinho et al., 2008).

2.2. Sociometric and clinical data and assessment of anxiety levels

For this part of the study, 44 patients were included. Gender, age, ethnicity and facial profile were evaluated. Ethnicity was evaluated through a self-report questionnaire. The facial profile was classified according to Capelozza Filho (2012) that have been used to determine facial phenotype in previous studies (Lauris et al., 2017; Queiroz et al., 2016; Siécola et al., 2017). Profile I corresponded to facial normality; Profile II was a facial profile in which there was a positive step between the maxilla and the mandible; and Profile III was a facial profile in which there was a negative step between the maxilla and the mandible. Individuals with Profile I presented with skeletal deformities, such as excessive or vertical maxillary deficiency, anterior open bite, and facial asymmetry, justifying the need for surgical intervention.

The anxiety levels of each individual were evaluated at three different times: 2 days before the surgical procedure (T1), 1 month postoperatively (T2), and 6 months postoperatively (T3). The STAI was used at all times. This scale, developed by Spielberger and collaborators in 1970, was translated and adapted for Brazil by Biaggio in 1979. This questionnaire is a scale composed of 20 objective questions that require the participant to indicate how "they usually feel" (Trait) and how they feel "at that very moment" (State). From the answers obtained, this scale has a specific scoring system: ranging from a total of 20–80 points, the higher the values obtained, the higher the trait- or state-anxiety in the patient.

2.3. DNA collection and genotypic analysis

For the genetic evaluation, patients with surgical complication that required a new intervention were excluded (n = 2). Therefore, 22 patients that returned for one month and 6 months for postoperative evaluation were included. Saliva samples were collected from them for genomic DNA extraction. The saliva collection and DNA extraction and purification were performed as previously described by Trevilatto and Line (2000).

For the genotypic analysis of the genetic polymorphisms of *ESR1* (*rs2234693* and rs9340799) and *ESR2* (*rs1256049* and rs4986938), the real time polymerase chain reaction (RT-PCR) technique was used by TaqMan™ (Biosystems) technology. The polymorphism characteristics in *ESR1* and *ESR2* are presented in Table 1.

2.4. Statistical analysis

Age was dichotomized, according to the median value, into two groups with values below and above the median.

Trait-anxiety and state-anxiety were tested for normal distributions with the Shapiro–Wilk test and demonstrated non-normal distributions. For non-normal variables, the median, minimum, and maximum variables were used. To compare the trait-anxiety and the state-anxiety between the times of evaluation, Friedman's Two-Way test and the Wilcoxon test were used. To evaluate the association between anxiety and the various variables, the Kruskal–Wallis test and the Mann–Whitney test were used. The data were analyzed with IBM SPSS software (Statistical Package for Social Science, USA) v24.0, with a significance level set at $p < 0.05$.

3. Results

Sixteen males and 28 females were included. The median age was 29 years, with a minimum of 18 years and a maximum of 52 years. Self-report ethnicity was represented for 68.2 % European Descendent and 31.8 % African American. According to the facial profile, 50% were classified as Profile III, 40% were classified as Profile II, and 10% were classified as Profile I.

The results between the anxiety levels and the different evaluation times are presented in Table 2. Patients had higher trait-anxiety and state-anxiety during the preoperative time period when compared to postoperative values at 1 month and 6 months ($p < 0.05$). When comparing the postoperative values at 1 month and 6 months, there was no statistical difference ($p > 0.05$).

The state-anxiety and trait-anxiety distributions for the preoperative time period are presented in Table 3. During the preoperative period, it was observed that females presented more trait-

Table 1
Candidate genes and polymorphisms that were studied.

Gene	Locus	Genetic polymorphism	MAF[a]	Base Change[a]
ESR1	6q25.1	rs2234693[b]	0.446	C/T
		rs9340799[c]	0.281	A/G
ESR2	14q23.2	*rs1256049*	0.129	C/T
		rs4986938	0.259	C/T

Note: MAF means minor allele frequency.
[a] Obtained from database: ncbi.nlm.nih.gov.
[b] Also known as PvuII.
[c] Also known as XbaI.

Table 2
Evaluation of the anxiety scores during the different time periods.

STAI	Preoperative	Postoperative (1 month)	Postoperative (6 months)	*P* value
	Median (min–max)	Median (min–max)	Median (min–max)	
Trait-anxiety	34 (21–62)[a]	31 (22–49)[b]	31 (20–53)[b]	**0.003**
State-anxiety	38 (25–89)[a]	30.5 (21–49)[b]	30.5 (20–51)[b]	**<0.001**

Note: The significance level is 0.05. Bold values indicate significance.
Friedman's Two-Way test and Wilcoxon test.

Table 3
Association between anxiety and the different variables during the preoperative time period.

Variables		Trait-anxiety	*P value*	State-anxiety	*P value*
		Median (min–max)		Median (min–max)	
Gender	Male	25 (21–29)	**0.005**[a]	32 (28–38)	0.140[a]
	Female	37 (22–54)		40 (27–45)	
Age	≤29	32 (23–54)	0.372[a]	36 (27–57)	0.655[a]
	>29	37 (21–54)		36 (28–65)	
Ethnicity	European	34 (21–54)	0.862	36 (28–65)	0.690[a]
	Descendent	–		–	
	African	39 (25–54)		34.5 (27–51)	
	American	–		–	
Facial Profile	I	43 (34–52)	0.366[b]	40.5 (30–51)	0.849[b]
	II	37 (22–54)		38.7 (29–57)	
	III	27 (21–54)		36 (27–65)	
rs2234693	CC	–	0.315[a]	–	0.105[a]
	CT	30.5 (21–54)		35.5 (27–49)	
	TT	37 (22–54)		41 (31–65)	
rs9340799	AA	37 (22–54)	0.079[a]	40 (31–65)	**0.046**[a]
	AG	27 (21–49)		32 (27–49)	
	GG	–		–	
rs1256049	AA	37 (21–54)	0.153[a]	38 (27–65)	0.307[a]
	AG	27 (23–29)		32 (29–38)	
	GG	–		–	
rs4986938	AA	35.5 (21–54)	0.446[b]	36 (28–49)	0.261[b]
	AG	29 (23–54)		40 (27–65)	
	GG	45 (37–53)		45.5 (41–50)	

Note: The significance level is 0.05. Bold values indicate significance.
[a] Mann-Whitney U test.
[b] Kruskal-Wallis test.

anxiety than males ($p = 0.005$). For the genetic polymorphism rs9340799, the AA genotype had median values that were higher than those of the AG genotype for state-anxiety ($p = 0.046$).

Tables 4 and 5 present the trait-anxiety and state-anxiety distributions at 1 and 6 months postoperatively. Gender remained associated with trait-anxiety during both time periods (p = 0.038 and p = 0.013, respectively).

4. Discussion

Dissatisfaction with facial appearance can lead a patient to seek treatment, including orthognathic surgery, in order to improve their condition (Santos et al., 2012). The demands and concerns about ending these complaints, questions over whether their quality of life and self-esteem will improve, as well as fear of exposure to the risks and complications that may occur both during and after surgery can lead an individual to present with higher levels of anxiety (Barel et al., 2018). In fact, in the present study, we were able to observe that anxiety levels were higher during the preoperative time period.

From the moment that a patient enters in a heightened state of anxiety, he or she is subjected to a stress response, and the hypothalamic-pituitary-adrenal axis is the main biological pathway of this condition (Bortoluzzi et al., 2015). Furthermore, Bortoluzzi et al. (2015) found that anxiety is a response to environmental stimuli, but it may also be related to other factors, including the individual genetic background of genes associated with this axis and sex-based hormones.

In our study, we were able to observe that women had higher anxiety levels than men across the 3 different time periods (preoperatively and 1 and 6 months postoperatively). Sex-based steroids are important for the regulation of emotions and behavior. They pass rapidly through the blood–brain barrier, and their receptors are abundant in brain areas (McEwen, 2001). Based on this, many research groups have shown the relationship of these hormones and their receptors to psychological disorders (Ryan et al., 2011; Westberg and Eriksson, 2008; Weickert et al., 2008; Gross and Hen, 2004; Comings et al., 1999).

Estrogen is a steroid hormone that presents in both genders. Estrogen affects the regulation, growth, and physiological development of the human reproductive system, in addition to directly influencing the neuroendocrine system. Estrogen is capable of altering neurotransmitter turnover, leading to a significant increase in serotonin and norepinephrine levels, which directly affect an individual's stress state and consequently increase anxiety levels. Estrogen depends on binding to the *ERα* and *ERβ* receptors in the target cells (Rezende, 2015). The genetic polymorphisms rs2234693 and rs9340799 are located at the splicing sites of *ESR1* and are the most studied so far, while for *ESR2,* the polymorphisms rs1256049 and rs4986938, located in the regulatory region, have been more commonly studied (Anghel et al., 2010). Therefore, we selected these 4 genetic polymorphisms as candidates to evaluate their associations with anxiety levels in patients undergoing orthognathic

Table 4
Association between anxiety and the different variables at 1 month postoperatively.

Variables		Trait-anxiety	*P value*	State-anxiety	*P* value
		Median (min–max)		Median (min–max)	
Gender	Male	25 (22–26)	0.038[a]	25 (21–30)	0.678[a]
	Female	35 (24–45)		32 (22–49)	
Age	≤29	32 (22–42)	0.289[a]	29 (31–37)	0.230[a]
	>29	31 (23–45)		27 (22–49)	
Ethnicity	European	29.5 (23–42)	0.369	29 (23–49)	0.363[a]
	Descendent	-		-	
	African	31 (22–45)		25 (21–37)	
	American	-		-	
Facial Profile	I	35.5 (35–36)	0.593[b]	41.5 (34–49)	0.197[b]
	II	31 (25–45)		28 (23–37)	
	III	28.5 (22–42)		26 (21–37)	
rs2234693	CC	-	0.842[a]	-	0.315[a]
	CT	31 (23–45)		27 (22–37)	
	TT	21 (24–42)		28 (23–37)	
rs9340799	AA	34 (22–42)	0.239[a]	30 (21–49)	0.443[a]
	AG	26 (23–45)		25 (22–37)	
	GG	-		-	
rs1256049	AA	33 (23–45)	0.118[a]	28 (22–37)	0.600[a]
	AG	26 (25–26)		25 (25–30)	
	GG	-		-	
rs4986938	AA	27 (23–45)	0.563[a]	30 (22–37)	0.887[a]
	AG	31 (24–42)		27 (24–35)	
	GG	36.5 (31–42)		29 (26–32)	

Note: The significance level is 0.05. Bold values indicate significance.
[a] Mann-Whitney U test.
[b] Kruskal-Wallis test.

Table 5
Association between anxiety and the different variables at 6 months postoperatively.

Variables		Trait-anxiety	*P value*	State-anxiety	*P value*
		Median (min–max)		Median (min–max)	
Gender	Male	25 (20–26)	0.013[a]	23 (20–30)	0.155[a]
	Female	33.5 (21–45)		31.5 (20–38)	
Age	≤29	30 (20–39)	0.348[a]	28.5 (22–35)	0.165[a]
	>29	33 (20–45)		32 (20–38)	
Ethnicity	European	32 (20–43)	0.551	31 (20–38)	0.502[a]
	Descendent	-		-	
	African	26 (20–45)		25 (22–36)	
	American	-		-	
Profile	I	-	0.708[b]	-	0.210[b]
	II	30 (21–45)		31.5 (20–36)	
	III	28.5 (20–37)		28.5 (20–34)	
rs2234693	CC	-	0.481[a]	-	0.481[a]
	CT	27.5 (20–45)		28.5 (20–36)	
	TT	33 (21–39)		31 (20–35)	
rs9340799	AA	35 (21–43)	0.322[a]	31.5 (20–35)	0.360[a]
	AG	26 (20–45)		27 (20–36)	
	GG	-		-	
rs1256049	AA	32 (20–45)	0.221[a]	31 (20–36)	0.307[a]
	AG	26 (25–26)		27 (22–30)	
	GG	-		-	
rs4986938	AA	27 (20–45)	0.408[b]	30.5 (20–36)	0.684[b]
	AG	31 (25–43)		27 (22–35)	
	GG	35 (33–37)		32 (31–33)	

Note: The significance level is 0.05. Bold values indicate significance.
[a] Mann-Whitney U test.
[b] Kruskal-Wallis test.

surgery. Wang et al. (2013) suggested that *ESR1* plays an important role in the biological effects of psychopathologies, highlighting its association with the genetic polymorphism rs9340799. Feng et al. (2017) also found an association between rs9340799 and anxiety, especially in AA homozygotes. They postulated that genetic polymorphism in ERs may modify their specific signaling, which leaves females more susceptible to these changes. In our study, we observed an association between the polymorphism rs9340799 in *ESR1* and state-anxiety and a borderline association between rs9340799 in *ESR1* and trait-anxiety during the preoperative period, in which the homozygous AA presented higher levels of anxiety.

Briefly, state-anxiety may lead patients to have higher levels of stress and may interfere with surgical treatment, their general health condition, and their final recovery and quality of life (Al-Bitar and Al-Ahmad, 2017; Nardi et al., 2003; Hunt et al., 2001). Actually, there is a new approach to use in individuals with dentofacial deformity known as “Surgery-First” (Mahmood et al., 2018)

that has shown improvements in the psychological aspects of patients reestablishing an early harmony of the face (Brucoli et al., 2019; Kanwal et al., 2018). However, this approach is not yet used in our service.

However, it is important to emphasize that our study has some obvious limitations. Our sociometric data is limited to the gender, age and ethnicity information. Also, the lack of the diagnosis of some conditions such as dysmorphophobia, could influence the outcome. Another important limitation is the fact that patients were not assessed previous and right after the orthodontic treatment, because of the characteristic of Our Service. There are some studies performed by a team of oral and maxillofacial surgeons with the same approach related to evaluation time (Brucoli et al., 2019; Hanafy et al., 2019; Kim et al., 2009; Takatsuji et al., 2015). Therefore, more studies should be performed in order to evaluate biomarkers for anxiety during orthognathic surgery, addressing the limitations of the present study, which would allow for better screening of more susceptible patients.

5. Conclusion

Gender and the genetic polymorphism rs9340799 in *ESR1* were associated with anxiety in orthognathic patients.

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Conflicts of interest

No author has any possible conflict of interest.

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