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Association between sleep quality and polymorphisms of the genes *COMT*, *HTR2A* and *FKBP5* in individuals with and without dentofacial deformity

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Sleep is a fundamental biological function, and any disturbances can lead to alterations in an individual's physical, occupational, cognitive, and social functioning. **Aim:** This study aimed to evaluate the quality of sleep and its association with factors such as age, sex, facial profile, and genetic polymorphisms in individuals who underwent dental treatment. **Methods:** The study comprised a total of 227 individuals. The "Sleep Assessment Questionnaire" was utilized to evaluate sleep quality. For the genetic assessment, oral mucosa cells were collected and markers from the *COMT* (*rs174675*, *rs165656*), *HTR2A* (*rs4941573*, *rs6313*), and *FKBP5* (*rs1360780, rs3800373*) genes were selected for real-time PCR analysis. The data were subjected to statistical analysis with a significance level of 0.05. **Results:** The results showed that women had a poorer perception of sleep quality ($p<0.05$). There was a significant association between sleep quality and facial profile ($p<0.05$). Individuals with facial profiles I and II had a poorer perception of sleep quality in general and in the domains of non-restorative sleep, sleep time disturbance, and restlessness. Individuals with facial profile II had a poorer perception of sleep apnea than those with profile III ($p=0.034$). There was a significant association between the *COMT rs174675* polymorphism and restlessness ($p=0.035$). **Conclusion:** The poorest perception of sleep quality was associated with women and individuals with facial profiles I and II. The poorest perception of restlessness was associated with *COMT* rs174675 polymorphism.

Keywords: Dentofacial deformities. Genetics. Sleep quality. Polymorphism, genetic.

Introduction

Sleep is a complex physiological process that continues to be one of the great enigmas of science[1]. Sleep quality and quality of life are closely related[2]. The International Classification of Sleep Disorders identifies approximately 90 disorders, such as snoring, obstructive sleep apnea/hypopnea syndrome, insomnia, narcolepsy, restless legs syndrome, among others[3].

The prevalence of sleep disorders is linked to various factors, including sex, age, education level, marital status, and employment[4]. Brockmann et al.[5], in 2016, conducted an assessment of the prevalence and associated factors of these disorders, revealing a high prevalence of sleep disorders among young adults. It is postulated that individuals with dentofacial deformities tend to perceive their sleep quality as poorer and that genetic associations may contribute to the onset of these deformities. Furthermore, individuals with polymorphisms linked to specific genes may exhibit heightened susceptibility to the development of these conditions[6].

The *5-HTR2A* genotype exhibited a significant association with sleep quality[7]. Conversely, the *FKBP5* gene, often referred to as the catastrophizing gene, is recognized as a primary risk factor for the onset of stress disorders, which subsequently lead to sleep disorders[8].

Sleep quality significantly influences an individual's physical, occupational, cognitive, and social functioning[1]. Hence, understanding and diagnosing the factors associated with sleep quality is crucial. This study aimed to evaluate sleep quality and its correlation with age, sex, facial profile, and genetic polymorphisms among individuals who received dental treatment at the University's Dentistry Clinic.

Materials and Methods

Ethical aspects

This research was approved by the Local Ethics Committee, under the CAAE protocol: 80846317.8.0000.0093, and complies with the principles of the Declaration of Helsinki for studies involving human subjects. All participants of the study signed an informed consent form.

Experimental design

A cross-sectional study was conducted involving 227 individuals who received dental treatment at the Dentistry Clinic of Universidade Positivo in Curitiba, Brazil. The recruitment process spanned from October 2018-2019.

The study participants were adults who received dental treatment at the University and consented to participate in the research by signing the informed consent form. The exclusion criteria were syndromic individuals, individuals orthodontically compensated, those with a previous history of orthognathic surgery and/or temporomandibular joint surgery and those with a previous history of facial trauma. All evaluations were carried out by previously trained examiners.

The sample size was calculated using OpenEpi[9], incorporating a 5% margin of error, an 80% power, and a 1:1 design effect. This calculation was predicated on the presence of sleep disturbance of 18.4%, as documented in a prior study by Machado et al.[10] (2020). Consequently, the calculation yielded a sample size of 227 participants.

The facial profile was classified according to the classification proposed by Capelozza Filho[11] (2004), based on the anteroposterior relationship between the maxilla and mandible. Individuals were grouped into three distinct facial profiles: profile I for those exhibiting a straight profile, profile II for those with a convex profile, and profile III for those demonstrating a concave profile. Trained examiners (KM, MM, EBF) conducted the facial profile evaluations.

Sleep quality assessment

The University of Toronto developed a simple screening tool, the "Sleep Assessment Questionnaire" (SAQ), to monitor primary sleep disorders in epidemiological studies and clinical practice[12]. Although these tools are predominantly international, few have been validated for the Portuguese language[13]. The SAQ, in particular, has been extensively utilized to establish associations between sleep disorders and conditions such as apnea[14,15].

The questionnaire comprises 17 questions designed to evaluate sleep experiences over the past 30 days. Responses are scored on a scale from 0 to 4, with the following point allocations: never = 0, rarely = 1, sometimes = 2, often = 3, and always = 4. These scores collectively categorize individuals based on the presence or absence of sleep disorders. A cutoff point of 16 was selected owing to its high sensitivity (0.73) and specificity (0.80). Consequently, participants with a total score ranging from 0 to 16 points were classified as "without sleep disturbance, " while those with a total score between 17 and 68 points were categorized as "with sleep disturbance".

Six domains are calculated using individual items: insomnia/hypersomnia (derived from the sum of questions 1, 2, and 3), sleep time disorder (derived from the sum of questions 4 and 8), sleep apnea (derived from the sum of questions 5 and 6), restlessness (based on question 7), non-restorative sleep (derived from the sum of questions 9, 10, and 11), and excessive daytime sleepiness (derived from the sum of questions 12 and 13). Questions 14, 15, 16, and 17 pertain to individual sleep habits[12,16-18].

Genetic evaluation

DNA was extracted from oral mucosa epithelial cells using a mouthwash of 5 ml of 3% glucose solution, with a 2-min rinse performed in duplicate, and gentle scraping of the cheek mucosa using a sterile wooden spatula[19]. The DNA was then purified using 10 M ammonium acetate and 1 mM EDTA[20] and stored at -20 ºC following a 2-day refrigeration period.

The DNA quantity and purity of each sample were determined using spectrophotometry (NanoDrop 1000, Thermo Fisher Scientific, US). DNA concentration was determined through readings at 260 nm. The purity was estimated using the ratio of 260 nm to 280 nm.

The selected genes for this study were *COMT*, *HTR2A*, and *FKBP5*. For COMT, the genetic markers utilized were *rs174675* (chr22:19946528, base change T>C, minimum allelic frequency T= 0.387) and *rs165656* (chr22:19961340, base change G>A/ G>C/G>T, minimum allelic frequency C= 0.409). The genetic markers of *HTR2A* were *rs4941573* (chr13:46890722, base change A>C / A>G, minimum allelic frequency G= 0.398) and *rs6313* (chr13:46895805, base change G>A, minimum allelic frequency A= 0.441) and of *FKBP5* were *rs1360780* (chr6:35639794, base change T>A / T>C, minimum allelic frequency T= 0.327) and *rs3800373* (chr6:35574699, base change C>A, minimum allelic frequency C=0.325).

The real-time PCR technique (QuantStudio™ 12K Flex Real-time PCR System) was used for genotyping, employing TaqMan ™ technology (Applied Biosystems).

Descriptive and inferential statistical analyses were applied to the data. The SAQ questionnaire scores were subjected to the Kolmogorov–Smirnov normality test, revealing non-normal behavior. Age was dichotomized using the median to assess the association with sleep quality. The Mann–Whitney or Kruskal–Wallis U test of independent samples was employed to assess associations between the SAQ, its domains, and clinical and genetic variables. A *p*-value of less than 0.05 was considered statistically significant. The IBM SPSS v.22.0® (Statistical Package for Social Science) computer program was used for data analysis.

Results

This study included 227 participants, comprising 150 women and 77 men. The median age of the participants was 26 years, ranging from 16 to 64 years. Out of these, 160 participants exhibited facial profile I without any dentofacial deformity. Meanwhile, 27 and 40 individuals presented with facial profiles II and III, respectively.

Regarding the presence of sleep disturbance, 76 (33.5%) and 151 (66.5%) participants were categorized as "without sleep disturbance" and "with sleep disturbance," respectively.

The study found no correlation between the sleep quality of participants and their age. Women perceived their sleep quality negatively than men in general SAQ and in the areas of non-restorative sleep, disturbed sleep schedule, daytime sleepiness, and restlessness ($p < 0.05$) (Table 1).

Table 1. Association between the perception of sleep quality with age and sex.

	Age			Sex		
SAQ	**≤ 26 years Median (IQR) (min -max)**	**> 26 years Median (IQR) (min-max)**	**p value**	**Male Median (IQR) (min-max)**	**Female Median (IQR) (min-max)**	**p value**
Overall score	20 (14-28) (0-58)	21(13-27) (0-58)	0.998	19.5 (13-24) (0-46)	22 (14-30) -58)	**0.017**
Sleeplessness	4 (2-6) (0-9)	4 (2-6) (0-10)	0.543	4 (2-5) (0-10)	4 (2-6) (0-9)	0.179
Non-restorative sleep	5 (3-7) (0-12)	5 (3-6) (0-12)	0.273	4 (3-6) (0-12)	5 (3-7) (0-12)	**0.023**

Continue

Continuation

Sleep time disturbance	2 (1-3) (0-8)	2 (1-3) (0-8)	0.842	2 (1-3) (0-6)	2 (1-4) (0-8)	**0.015**
Daytime sleepiness	1 (0-2) (0-8)	2 (0-2) (0-7)	0.825	1 (0-2) (0-5)	2 (0-2) (0-8)	**0.002**
Sleep apnea	0 (0-2) (0-8)	1 (0-2) (0-8)	0.740	1(0-2) (0-8)	0 (0-2) (0-8)	0.592
Restlessness	1 (0-2) (0-6)	1 (0-2) (0-4)	0.210	1 (0-2) (0-4)	1 (0-2) (0-6)	0.030

Note: Mann-Whitney U test of independent samples with a significance of 0.05.

The Kruskal–Wallis test revealed a correlation between facial profile types and perceived sleep quality. Participants with facial profile II reported a poorer perception of sleep quality overall, particularly in domains related to non-restorative sleep, disturbed sleep time, and restlessness, compared to those with facial profile III (p <0.05). Similarly, individuals with facial profile I, who had no deformity, also reported a poorer perception of sleep quality in these domains compared to those with facial profile III. Furthermore, individuals with facial profile II reported a poorer perception in the domain concerning sleep apnea compared to those with facial profile III (p = 0.034) (Table 2).

Table 2. Association between the perception of sleep quality and facial profile.

SAQ	**Profile**			**p value**
	I Median (IQR) (min -max)	**II Median (IQR) (min -max)**	**III Median (IQR) (min -max)**	
Overall score	21.5 (15-27)[a] (0-68)	26 (20-33)[a] (5-52)	16 (10-20)[b] (0-43)	**0.001**
Sleeplessness	4 (2-6) (0-9)	5 (3-6) (0-8)	4 (2-5) (0-10)	0.154
Non-restorative sleep	5 (3-7)[a] (0-12)	6 (4-7)[a] (0-10)	3 (2-5)[b] (0-12)	**0.006**
Sleep time disturbance	2 (1-2)[a] (0-8)	3 (1-4)[a] (0-8)	2 (1-2)[b] (0-4)	**0.007**
Daytime sleepiness	1 (0-2) (0-8)	2 (1-2) (0-4)	1 (0-2) (0-5)	0.161
Sleep apnea	0.5 (0-2)[ab] (0-8)	2 (0-4)[a] (0-8)	0 (0-2)[b] (0-8)	**0.034**
Restlessness	1 (0-2)[a] (0-4)	2 (1-2)[a] (0-6)	0 (0-1)[b] (0-2)	**0.001**

Note: Kruskal-Wallis test With significance a of 0.05. The pairwise comparison was performed with the Mann-Whitney test. * Different superscript letters indicate statistical differences in peer comparisons.

During the genetic evaluation, an association was observed between the *rs174675* polymorphism of *COMT* and the domain associated with restlessness. Individuals with homozygous C demonstrated a poorer perception of sleep quality in this domain compared to heterozygous CT individuals (p = 0.035). No association was found between SAQ and the other genetic markers analyzed (Table 3).

Table 3. Association between genetic polymorphisms and the perception of sleep quality.

HTR2A								
Sleep quality	rs6313 Median (IQT) (min-max)			p Value	rs4941573 Median (IQT) (min-max)			p Value
	CC	CT	TT		CC	CT	TT	
Overall score	21 (16-27) (0-52)	20.5(12-28) (0-58)	22 (15-29) (3-56)	0.732	21 (15-29) (5-53)	21 (12-28) (0-58)	20 (16-27) (0-43)	0.812
Sleeplessness	4 (2-6) (0-9)	4 (2-6) (0-10)	4 (3-6) (0-8)	0.599	4 (3-6) (0-9)	4 (2-5) (0-10)	4.5 (2-6) (0-9)	0.187
Non-restorative sleep	5 (4-6) (0-11)	5 (3-7) (0-12)	5 (3-7) (0-12)	0.986	5 (3-7) (0-12)	5 (3-7) (0-12)	5 (3-6) (0-11)	0.972
Sleep time disturbance	2 (1-4) (0-8)	2 (1-3) (0-7)	2 (1-3) (0-6)	0.477	2 (1-4) (0-6)	2 (1-3) (0-8)	2 (1-3) (0-6)	0.635
Daytime sleepiness	1 (0-2) (0-5)	1 (0-2) (0-7)	1 (0-2) (0-8)	0.539	1 (0-2) (0-8)	1 (0-2) (0-7)	1 (0-2) (0-5)	0.338
Sleep apnea	0 (0-2) (0-8)	1 (0-2) (0-8)	0 (0-2) (0-6)	0.874	1(0-3) (0-6)	0 (0-2) (0-8)	1 (0-2) (0-7)	0.782
Restlessness	1 (0-2) (0-4)	1 (0-2) (0-6)	1 (0-2) (0-4)	0.582	1 (0-2) (0-4)	1 (0-2) (0-6)	1 (0-2) (0-3)	0.198

COMT								
Sleep quality	rs165656 Median (IQT) (min-max)			p Value	rs174675 Median (IQT) (min-max)			p Value
	CC	CT	TT		CC	CT	TT	
Overall score	20.5 (15-27) (0-43)	21(13-27) (0-58)	19.5 (15-33) (5-56)	0.931	21 (15-28) (0-58)	19 (13-24) (5-35)	22.5 (13-37) (11-46)	0.338
Sleeplessness	4 (2-6) (0-10)	4 (2-5) (0-9)	4 (2-6) (0-9)	0.775	4 (2-6) (0-10)	4 (2-5) (0-9)	4 (2-7) (2-7)	0.934
Non-restorative sleep	5 (3-7) (0-10)	5 (3-7) (0-12)	4 (3-7) (0-12)	0.868	5 (3-7) (0-12)	4 (3-6) (0-9)	5.5 (3.5-8.5) (2-12)	0.188
Sleep time disturbance	2 (1-3) (0-8)	2 (1-4) (0-7)	2 (1-4) (0-8)	0.336	2 (1-4) (0-8)	2 (1-3) (0-6)	1.5 (0.5-4) (0-5)	0.831
Daytime sleepiness	2 (0-2) (0-5)	1 (0-2) (0-7)	2 (0-2) (0-8)	0.236	1 (0-2) (0-8)	1 (0-2) (0-5)	2 (1.5-3) (0-4)	0.299
Sleep apnea	0.5 (0-2) (0-8)	0 (0-2) (0-8)	0.5 (0-2) (0-8)	0.990	1 (0-2) (0-8)	0 (0-2) (0-4)	1.5 (0-4) (0-7)	0.343
Restlessness	1 () (0-6)	1 () (0-4)	1 () (0-4)	0.915	1 (0-2) (0-6)[a]	0 (0-1) (0-3)[b]	1 (0.5-3) (0-4)[ab]	0.035

FKBP5								
Sleep quality	rs1360780 Median (IQT) (min-max)			p Value	rs3800373 Median (IQT) (min-max)			p Value
	CC	CT	TT		CC	CT	TT	
Overall score	22 (13-29) (0-58)	20(14-25) (0-46)	20 (15-27) (5-45)	0.546	22 (13,5-29) (0-58)	20 (14-27) (0-56)	22 (11-27) (5-45)	0.748
Sleeplessness	4 (2-6) (0-10)	4 (2-5) (0-9)	4 (3-6) (2-8)	0.422	4 (2-6) (0-10)	4 (2-5) (0-9)	5 (3-6) (2-8)	0.311
Non-restorative sleep	5 (3-7) (0-12)	5 (3-6) (0-12)	5 (3-7) (0-12)	0.857	5 (3-7) (0-12)	5 (3-7) (0-12)	5 (3-7) (0-12)	0.961
Sleep time disturbance	2 (1-3) (0-8)	2 (1-3) (0-8)	3 (1-4) (0-5)	0.338	2 (1-4) (0-8)	2 (1-3) (0-8)	3 (1-3) (0-5)	0.627
Daytime sleepiness	1 (0-2) (0-8)	2 (0-2) (0-7)	1 (0-2) (0-5)	0.316	1 (0-2) (0-6)	2 (0-2) (0-8)	1 (0-2) (0-5)	0.182
Sleep apnea	0.5 (0-3) (0-8)	0 (0-2) (0-8)	0 (0-2) (0-4)	0.564	1(0-2.5) (0-8)	1 (0-2) (0-8)	0 (0-1.5) (0-4)	0.478
Restlessness	1 (0-2) (0-6)	1 (0-1) (0-4)	1 (0-2) (0-4)	0.228	1 (0-2) (0-6)	1 (0-2) (0-4)	1 (0-1.5) (0-4)	0.336

Note: Kruskal-Wallis test With significance a of 0.05. The pairwise comparison was performed with the Mann-Whitney test. * Different superscript letters indicate statistical differences in peer comparisons.

Discussion

This study assessed sleep quality and its correlation with factors such as age, sex, facial profile, and genetic polymorphisms in individuals who received dental treatment at the University's Dentistry Clinic. The findings indicated that women and individuals with a type II facial profile perceived their sleep quality to be poorer. Additionally, a notable association was observed between *the COMT rs174675* polymorphism and restlessness.

Barros et al.[21] (2019) carried out a Health Survey in Campinas, São Paulo, Brazil. Their findings confirmed an association between sleep quality, sex and age group. The prevalence of poor self-assessed sleep quality was 29.1% and it was significantly higher in women aged 40 to 50 years. However, in our study, sleep quality did not correlate with age. However, women reported a poorer perception of sleep quality compared to men.

Several other studies have also reported a higher prevalence of poor sleep quality among women. This observation can be attributed to the fact that women generally report more health issues than men. Additionally, hormonal fluctuations associated with pregnancy, menopause, and menstrual cycles could further contribute to this trend[22-24].

The quality of sleep and its associated disorders have been linked to different facial profiles. Several studies, including Brevi et al.[25], 2015, Boyd[26], 2009, and George et al.[27], 2007, have found that individuals suffering from sleep apnea often exhibit a retrusive profile, also known as facial profile II. Approximately 58% of individuals with sleep apnea have micrognathism or mandibular retrognathism[28]. Our study supported these findings, indicating that individuals with facial profile II have a poorer perception of sleep quality and a higher prevalence of sleep apnea compared to those with facial profile III.

We discovered that individuals with facial profiles I and II perceived their sleep quality to be poorer than those with facial profile III. This outcome may be linked to the overrepresentation of individuals with facial profile I in the sample. Additionally, we hypothesized that for individuals with facial profile III, other functional issues may have a greater impact than sleep quality.

According to Jiang et al.[7] (2016), the serotonin receptor (*5-HTR*) plays a key role in regulation of sleep quality. Our results indicated that this gene functioned as expected, as it was not associated with poorer sleep quality.

The *COMT* gene is responsible for regulating dopamine. A deficiency in this catecholamine can lead to concentration issues, alterations in sleep and libido, mood swings, impulsiveness, and aggression, all of which can negatively impact sleep quality irrespective of facial profile[29]. Our findings align with this, as we discovered a correlation between sleep quality and the *COMT* gene, particularly in the realm of restlessness.

The increased expression of *FKBP5* gene, often referred to as the catastrophizing gene, is widely recognized as a significant risk factor in the development of stress disorders, which in turn can lead to sleep disorders. However, our study found no correlation between sleep quality and the polymorphism of this gene.

The primary limitation of this study was the absence of additional complementary tests to assess sleep quality and disorders, such as the polysomnography exam. This test monitors brain, muscle, cardiac, ocular, and respiratory activity, as well as oxygen saturation throughout the night. The outcomes of this examination delineate sleep architecture, duration, timing, respiratory obstruction, and abnormal limb movements, which could potentially correlate with SAQ results. Despite the promising nature of the SAQ, it is a self-perception test and necessitates meticulous understanding and interpretation.

In conclusion, the perception of poor sleep quality was associated with women and individuals with facial profile I and II. The worse perception of sleep apnea was linked to individuals with facial profile II. Moreover, the perception of heightened restlessness was associated with individuals possessing the *COMT rs174675* polymorphism.

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Conflicting Interest

There are no conflicts of interest

Data Availability

Datasets related to this article will be available upon request to the corresponding author.

Author Contribution

Elvira K. B. Flores: Acquisition and analysis of data for the work, drafting the work and reviewing, final approval of the manuscript. **Marina Fanderuff:** Analysis of data for the work, drafting the work and reviewing, final approval of the manuscript. **Katheleen Miranda dos Santos:** Acquisition and analysis of data for the work, final approval of the manuscript. **Michelle N. Meger:** Acquisition and analysis of data for the work, final approval of the manuscript. **Delson J. da Costa:** Drafting the work and reviewing, final approval of the manuscript. **Carmen L. M. Storrer:** Design of the work, drafting the work and reviewing, final approval of the manuscript. **Rafaela Scariot:** Design of the work, drafting the work and reviewing, final approval of the manuscript. All authors actively participated in the manuscript's findings, have revised and approved the final version of the manuscript.

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