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Disturbance of Nocturnal Secretion of Melatonin and Sleep, in Chronic Obstructive Pulmonary Disease

Monserrat Martínez-Luna[1], José E. Meza Alvarado[2], Ricardo I. Lázaro Pacheco[3], Jaime Morales-Romero[4] and Manuel Ángeles-Castellanos[5]*

[1, 2,5]*Institute of Biomedical Sciences. Universidad Veracruzana. 91190, Veracruz, México.*

[3]*Centro de Especialidades Médicas del Estado de Veracruz "Dr. Rafael Lucio" (CEMEV), Ruiz Cortines 2903, 91020, Veracruz, México.*

[4]*Faculty of Medicine. Universidad Nacional Autonoma de Mexico, Av. Universidad 3000, 04510, Mexico, Mexico*

***Corresponding author**

Manuel Ángeles-Castellanos, Departamento de Anatomía, Edificio B 4º Piso Fac de Medicina, UNAM. México City 04510, México, Tel: 5255-5623-2422, Email: mangeles_castellanos@unam.mx

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Keywords

- Circadian rhythms
- Sleep disturbances
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Abstract

The respiratory symptoms of Chronic Obstructive Pulmonary Disease (COPD), these are most acute during the night, altering the sleep-wake cycle, which is synchronized by melatonin, this hormone is inhibited by light exposition during the night, generating daytime sleepiness, decreased alertness, sleep problems and poor quality of sleep quality. In this study we determined, daily concentration of salivary melatonin and its possible effect on sleep quality in patients. Fifty-five patients divided into groups were studied: COPD (n=26) and control (n=29). Sleep quality was assessed by Epworth and Pittsburgh questionnaires. Melatonin concentrations were quantified at 4 temporal points throughout the day and quantified by ELISA method. The mean Epworth questionnaire score in the COPD group was 10.11 ± 3.93 and control 5.5 ± 2.66 ($p<0.001$). Patients with COPD presented daytime somnolence than patients in the control group. In the Pittsburgh questionnaire a significant difference was observed, the mean score in the COPD group was 12.38 ± 3.45 and in the control, it was 7.96 ± 2 ($p<0.001$), although both groups present poor sleep quality, it was higher in COPD patients. Melatonin analysis indicated significant differences between groups ($F(1,244) = 36.0598$; $p<0.0001$), with lower values in the COPD group. COPD patients lost the daily pattern with melatonin levels and poor sleep quality. These results suggest that the nocturnal manifestations of COPD and the patient's management of the disease negatively impact melatonin secretion and its ability to regulate sleep, which should be considered in the management of this disease.

ABBREVIATIONS

COPD: Chronic obstructive pulmonary disease, MEL: Melatonin, FEV1/FVC: The proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC), BMI: Body Mass Index, ANOVA: Analysis of Variance, PSQI: Pittsburgh Sleep Quality Index.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a chronic degenerative disease and a worldwide public health problem [1], its growth rate is accelerated by the aging of the population and continued exposure to risk factors (chronic exposure to biomass, smoking and pollution) [2-3]. It is characterized by respiratory symptoms such as cough, dyspnea, expectoration, chest tightness and wheezing, as well as limited airflow due to prolonged exposure to noxious particles or gases that distort the brachial architecture leading to concentric airway obstruction [4-5].

Some studies have confirmed that COPD patients have poor sleep quality, manifesting difficulties in initiating sleep, frequent awakenings and increased excessive daytime sleepiness [6-7]. Sleep is regulated by the circadian system and modulated by the melatonin hormone (MEL). MEL is synthesized mainly by the pineal gland, and with a circadian pattern of release [8], its highest concentration occurs during the night inducing a decrease in neurobehavioral activity favoring adequate sleep [9-10]. It has been shown that with the administration of exogenous melatonin in patients with COPD, the quality of sleep improves [11-13]. However, these studies have not measured nocturnal melatonin concentrations. During the night, COPD symptoms become more acute, and their management involves exposure to light sources in the bedroom, which leads to the interruption of endogenous melatonin secretion. Likewise, sleep-wake cycle patterns are affected, which is reflected in poor sleep quality [14]. The aim of this study was to determine the alterations in the release and concentration of melatonin in saliva, as well as its correlation with indicators of sleep quality in patients diagnosed with COPD.

MATERIALS AND METHODS

Ethics

This protocol was authorized by the Research and Research Ethics Committees of the Dr. Rafael Lucio High Specialty Center

Hospital, Xalapa, Veracruz (30-CEI-001-20170221) and the Faculty of Medicine of the National Autonomous University of Mexico (137SR-2019). This study is considered minimal risk in accordance with the provisions of the General Health Law on research for health, Mexico. All patients voluntarily participated in the study and signed a letter of informed consent, and the principles of the Declaration of Helsinki [15] were met.

Subjects

Using consecutive case sampling, from July 01, 2018, to December 30, 2019; in total 55 of 67 patients who met the inclusion criteria and attended the pulmonology outpatient clinic of the Dr. Rafael Lucio High Specialty Center were included.

Subjects older than 40 years, with a history of biomass exposure or smoking and a diagnosis of COPD, were included. Exclusion criteria were patients with a diagnosis of asthma, obstructive sleep apnea syndrome or other respiratory disease different or additional to COPD. Personal data such as name, sex, age, weight, and schooling were collected and recorded in a data format, maintaining confidentiality.

Exposure to risk factors

We measured the history of exposure to conditions that in previous studies have been defined as risk factors for COPD: 1) exposure to wood smoke or 2) history of smoking [16]. Patients who responded affirmatively to the antecedent of exposure to wood smoke were asked the duration of exposure in years and its intensity (number of hours per day), and the biomass exposure index was calculated with the following formula: hours per day exposed to wood smoke by years [17]. On the other hand, patients who responded affirmatively to the smoking history were asked the intensity (number of cigarette packs smoked per day) and the duration in years and the smoking index was calculated with the following formula: [(number of cigarettes smoked per day) X (years of smoking)]/20, [18].

Diagnosis of COPD

For the diagnosis of COPD, each patient underwent spirometry with the Care Fusion® brand Micro 1 (portable) equipment, previously calibrated, complying with ATS/ER quality standards. To perform the spirometry, the patient was seated, with his back straight, without crossing his legs and using nose clips to avoid air loss. The patient was instructed how to place the mouthpiece of the device between the lips at the time of inspiration for proper technique. The test was concluded with each patient when three valid and reproducible results were obtained. Between each attempt, the patient was allowed to rest and only a maximum of eight attempts were allowed, if after the eight attempts no reproducible results were obtained, the patient was discarded from the study. With the results of the spirometry and the risk factor exposure index, the diagnosis of COPD was obtained and the patients with FEV_1/FVC ratio value less than 70% were included in the COPD group and the control group was made up of patients with FEV_1/FVC values greater than 70% [4].

Evaluation of sleep quality

Sleep quality was assessed by two questionnaires applied to all participants in a face-to-face manner by an interviewer. The Pittsburgh Sleep Quality Index (PSQI) that assesses sleep quality through seven components and the Mexican Version of the Epworth UNAM/UAM Sleepiness Scale that assesses the propensity to fall asleep in eight different sedentary situations. Both instruments have been used and validated in the Mexican population [19,20].

Measurement of melatonin and salivary cortisol

To determine the daily rhythm of melatonin and cortisol release, the concentrations of both hormones in saliva were quantified. For this purpose, salivary samples were requested from the patients at four times throughout the day at 07:00, 13:00, 19:00 and 01:00 h. For sample collection, patients were provided with four wide-mouth plastic bottles with screw caps, properly labeled, indicating the time of sample collection and the patient's name. They were also given instructions with the basic indications for obtaining representative samples, such as not eating, drinking, or brushing their teeth 30 min before taking the sample. It was emphasized that the sample to be deposited should be only saliva in a minimum volume of 0.5mL. Samples containing blood or sputum were discarded. Once the samples were obtained, they were refrigerated at 4 °C, and then stored at -20 °C until the total number of samples was completed for processing. They were then analyzed using a commercial kit for each hormone (Enzyme Immunoassay for the direct, quantitative determination of melatonin or cortisol in human saliva, IBL International cat. No 54041). Samples were processed in duplicate following the manufacturer's recommendations.

Statistical analysis

The normality of the data was examined in the StatPlus Build 7.3.3/Core v7.3.32 program using the Shapiro-Wilk test. The following variables were compared between the COPD group and the control group: age, body mass index, Epworth Sleepiness Scale score and Pittsburgh Sleep Quality Index. Continuous variables were compared by *Student's t-test* or *Mann-Whitney U-test* according to their distribution, while categorical variables were compared by *Fisher's* exact test. Subjects with good and poor sleep quality were compared between the COPD and control groups using the *chi-square test*; meanwhile, the components of the Pittsburgh Sleep Quality Index were compared using the *Mann-Whitney U test*.

Cortisol and melatonin levels were analyzed with a two-way ANOVA, followed by a post hoc Tukey test. Significant values were considered when $p < 0.05$. On the other hand, with Spearman's correlation analysis a matrix was performed where the values of melatonin and cortisol in saliva measured at 1:00, 7:00, 13:00 and 19: 00 h, Pittsburgh Sleep Quality index score, Epworth sleepiness scale score, smoking index, biomass pollutant exposure score, ratio, FEV_1/FVC schooling in ordinal scale, and age in years. All analyses were performed with the statistical program IBM SPSS Statistics version 25.

RESULTS

Sixty-seven patients were identified who met the inclusion criteria for participation in the study. However, seven dropped out of the study, three did not comply with the medical indications, one did not provide the requested saliva samples and

one was unable to perform the spirometry maneuvers (Figure 1). Finally, 55 patients were studied, divided into the COPD group n = 26 and control n = 29, with a mean age of 69 ± 9 years; of these, 71% were women and 29% were men. There were no significant differences between the COPD and control groups with respect to age, BMI, sex, and schooling (Table 1).

Sleep Quality

The median score obtained on the Pittsburgh Sleep Quality Index was significantly higher in the COPD group than in the control ($p < 0.001$) (Figure 2). Except for the use of hypnotic medication, similar results were found when comparing the components of this index between the comparison groups (Table 2).

The patient's tendency to fall asleep in eight different situations of daily life was evaluated, the mean score obtained from the COPD patient group was 10.11 ± 3.93 points and in the control group 5.5 ± 2.66 points. Analysis with *Student's t-test* showed that the values of the COPD group compared to the control group were significant, [t = -5.082, p < 0.001] (Figure 3).

In the probability analysis, subjects with a history of biomass exposure had a slightly increased risk of COPD, although not significant (OR = 1.3, $p = 0.76$). Subjects with poor sleep quality also showed a non-significant increased risk of COPD (OR= 3.1, $p = 0.25$) (Table 3).

Salivary cortisol

In both groups, salivary cortisol levels were determined every 6 hours throughout a 24h cycle, two-way ANOVA analysis revealed the presence of a daily rhythm of secretion with elevated values at 07:00 h, with no significant difference considering the COPD condition between the studied groups (F (1.244) = 0.4066; $p > 0.05$). However, a significant effect was identified by the time factor (F (3.244) = 25.6256; $p<0.0001$) and by the interaction between group by time (F (3.244) = 42.67; $p < 0.05$] (Figure 4).

Salivary melatonin

In both groups, salivary melatonin levels of determined every 6 hours throughout a 24h cycle, two-way ANOVA analysis revealed significant differences by COPD condition between groups (F (1. 244) = 36.0598; p<0.00001), observing a significant effect by the time factor (F (3.244) = 36.6025; p<0.0001) and by the interaction between group by time (F (3.244) = 33.2778; p<0.00001] (Figure 5).

The correlation analysis between all variables (Table 4), a significant correlation was found between melatonin levels measured at 01:00 h with the following variables: negative correlation with the Pittsburgh Sleep Quality Index (Rho = -0.30, $p = 0.027$) indicating that the lower the melatonin concentration the higher the score on the Sleep Quality index. A negative correlation was also identified with the Epworth Sleepiness Scale (Rho= -0.41, $p = 0.002$), observing a higher scale score when melatonin concentrations are low. Additionally, a positive correlation was found with the percentage of the FEV_1/FVC ratio (Rho= 0.61, $p < 0.001$), indicating that patients with lower percentage in the FEV_1/FVC ratio present lower melatonin concentrations at 01:00 h. Other correlations were found between the FEV_1/FVC value that correlates negatively with the Pittsburgh Sleep Quality Index score (Rho= -0.61, $p < 0.001$) as well as with sleepiness measured with Epworth (Rho= -0.60, $p < 0.001$), indicating that patients with greater pulmonary obstruction, manifest poor sleep quality.

DISCUSSION

The results obtained in this study demonstrate that COPD patients have poor sleep quality and low nocturnal melatonin

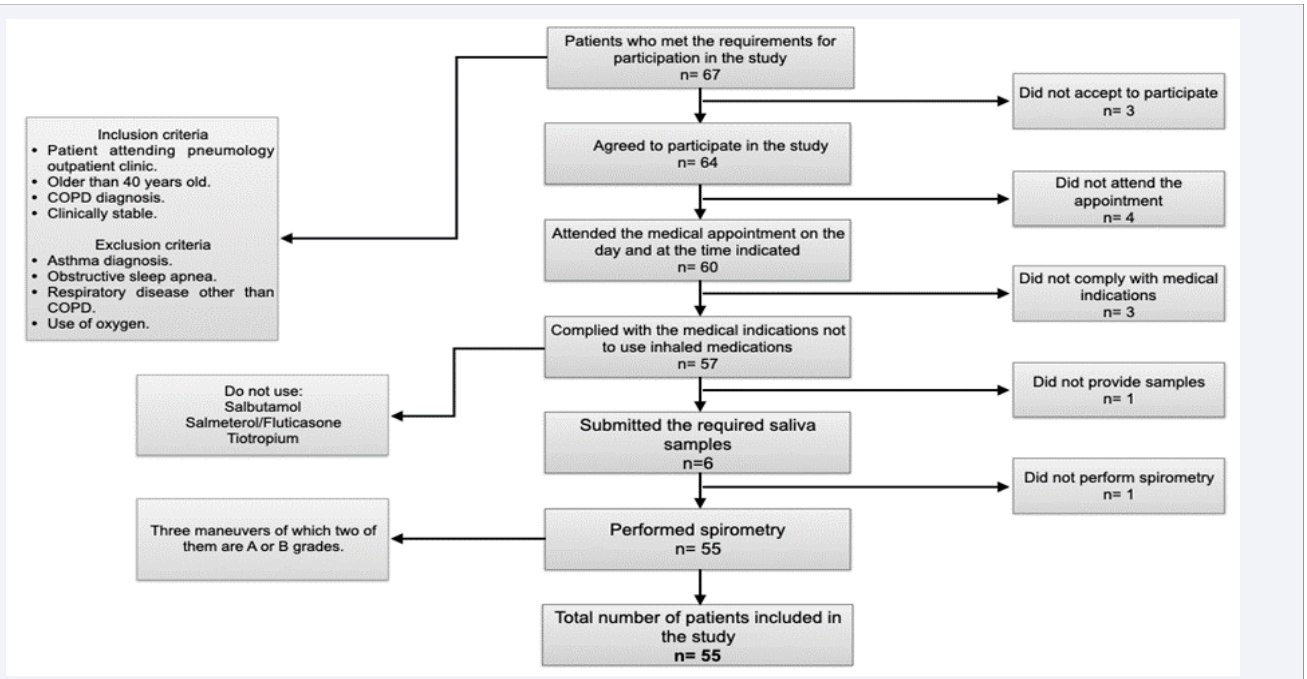

Figure 1 Description of the process for integrating participants and obtaining samples.

Table 1: Demographic characteristics of the study groups.

Demographic characteristics	EPOC n= 26	Control n= 29	*P*
Age (years)	71 ± 8.9	67 ± 9.4	0.07
BMI (kg/m^2)	28 ± 4.1	28 ± 5.2	0.13
Sex (Female/Male) Schooling, n (%)	18/8	21/8	0.41
No Schooling	4 (15)	6 (21)	0.66
Basic	14 (54)	13 (45)	0.73
High school	5 (19)	6 (21)	0.64
Higher	3 (12)	4 (13)	0.59

BMI = body mass index. Data for age and BMI are presented as means ± SD.
Sex and schooling are presented as individuals per group.
Age, BMI and sex variables were analyzed with Student's t test. Schooling was analyzed with the Mann Whitney U test.

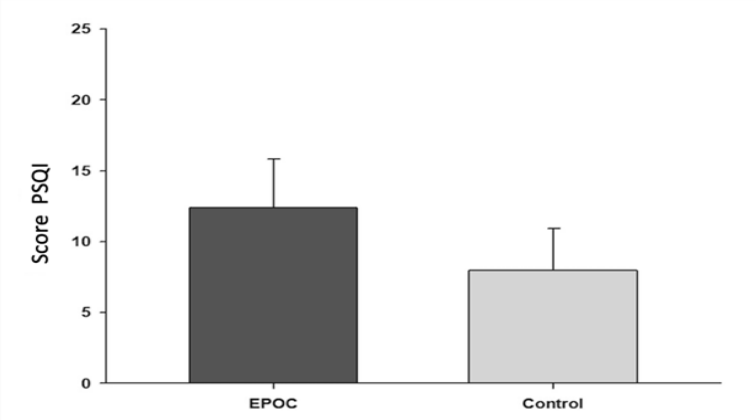

Figure 2 Comparison between groups for the Pittsburgh Sleep Quality Index score, using the Mann Whitney U test, the statistical difference was not significative (N.S); Values are represented as mean ± SD.

Table 2. Comparative analysis of sleep components obtained from the Pittsburgh Sleep Quality Index questionnaire.

Variable	EPOC *n* = 26			Control *n* = 29			
	Percentiles			Percentiles			
	25	50	75	25	50	75	*p*-value
Subjective sleep quality	1.75	2.00	3.00	1.00	1.00	2.00	< 0.001
Sleep latency	2.00	2.00	3.00	0.50	2.00	2.00	< 0.001
Duration of sleep	2.00	2.00	3.00	1.00	1.00	2.00	0.001
Sleep efficiency	1.00	2.00	3.00	0.00	1.00	2.00	0.004
Sleep disturbances	2.00	2.00	2.00	1.00	2.00	2.00	0.006
Use of hypnotic medication	0.00	0.00	0.00	0.00	0.00	0.00	0.926
Daytime dysfunction	1.00	2.00	3.00	1.00	2.00	2.00	0.046

Data are expressed by group, 25, 50 and 75 percentiles (Mann Whitney U test).

concentrations. Several studies have reported the frequent complaint of COPD patients with poorer quality sleep [21-23]. However, melatonin concentrations in these patients had not been studied to date. This is the first study to determine that sleep disturbance in COPD patients is probably a consequence of multiple factors, including nighttime symptoms such as cough and dyspnea and the administration of medications that promote exposure to artificial light, which induces a decrease in melatonin secretion [12, 24], a hormone that modulates the sleep-wake cycle.

Several investigations have evaluated the quality of sleep-in patients with COPD [23, 25-26] and it is estimated that approximately 60 to 70% of these patients have poor sleep quality [6, 25]. The results of the present study indicate that both groups had poor sleep quality. This could be due to the age of the patients, considering that as people age, the sleep pattern

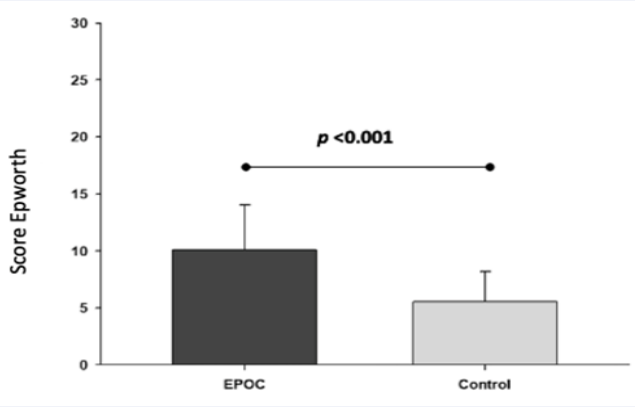

Figure 3 Comparison of the groups studied of the global score of the Epworth Sleepiness Scale using Student's t-test. P<0.001; Values are represented as mean ± SD.

Table 3. Comparison of previous exposure to risk factors and sleep quality between the groups studied.

	EPOC *n* = 26	Control *n* = 29	OR (IC95 %)	*p*-value
Previous exposure, n (%) Biomass	20 (76.9)	21 (72.4)	1.3 (0.4 a 4.3)	0.76
Tobacco	6 (23.1)	8 (27.6)	1	
Sleep quality, n (%) Poor quality	24 (92.3)	23 (79.3)	3.1 (0.6 a 17.1)	0.25
Good quality	2 (7.7)	6 (20.7)	1	

Comparison of proportions by Fisher's exact test.
OR: odds ratio.
95%CI: 95% confidence intervals.
Reference group: OR = 1.

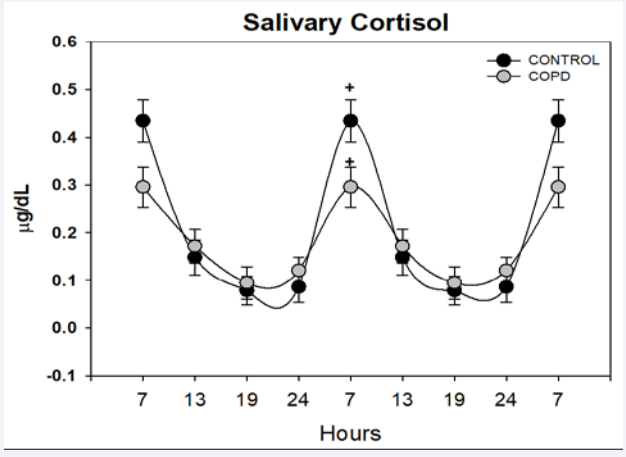

Figure 4 Circadian pattern of cortisol levels in both groups of patients. (+) indicates temporal difference throughout the day in both groups (P<0.05). But there is no statistical difference between groups.

is modified, increasing the stages of light sleep, and decreasing the stages of deep sleep, a phenomenon known as fragmentation of sleep due to aging. This is manifested by difficulties in falling asleep and staying asleep, due to frequent awakenings [27]. A similar study identified that patients with COPD and controls manifested poor sleep quality, although patients with COPD increased the prevalence to 36% with mean scores of 5.1 on the PSQI scale. In contrast to our study, we found that the COPD group increased to 92% of patients with poor sleep quality with PSQI scores of 12.3828, showing an increase in symptomatology manifestations. The variables analyzed such as age, sex, and BMI of the patients in both studies were similar, although they differed in terms of risk factors for developing COPD, since they included patients with a history of smoking and our study included patients with a history of smoking and exposure to biomass. This suggests that the differences in sleep quality could be due to the different habits and lifestyle of patients in these populations.

Evaluation of the PSQI components showed that 46% of patients in the COPD group had poor sleep latency of 60 min and 58% with low sleep duration of 5 to 6 hours, being the two main components affected with higher scores. As a result of poor sleep quality in COPD patients, a four-fold increase in daytime sleepiness compared to controls was identified when assessing daytime sleepiness. Observing a positive correlation between PSQI and Epworth scores, like those reported in other investigations. Concluding that in most patient's, daytime sleepiness is caused by poor sleep quality and even by nocturnal dyspnea in patients [29-31].

On the other hand, in this study one of the objectives was the determination of nocturnal melatonin levels and the exploration of a correlation with poor sleep quality. Considering that an alternative to treat poor sleep quality in COPD patients, oral administration of 3 mg of exogenous melatonin one hour before bedtime for 21 days has been used. The results based on PSQI evaluations show an improvement in the group treated with melatonin, compared to the group that received placebo, suggesting that melatonin has an important role in the sleep quality of these patients [11-13]. Considering that melatonin is a hormone with nocturnal release, it could be altered in these

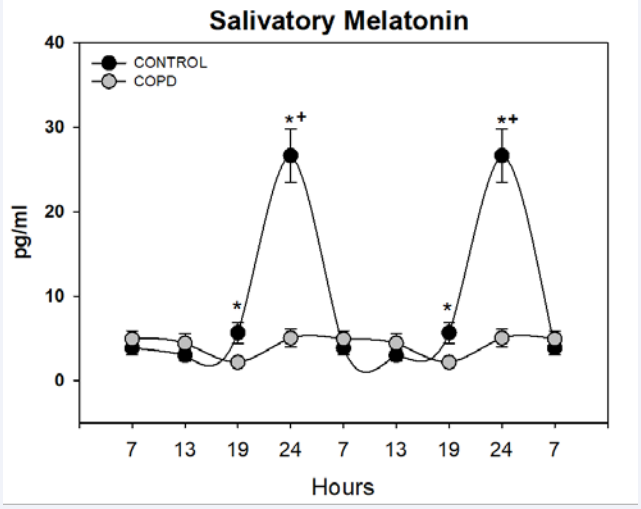

Figure 5 Circadian pattern of melatonin levels in both groups of patients. Asterisk indicates statistically significant differences between groups (P < 0.00001). (+) indicates temporal difference throughout the day in the control group (P<0.0001).

Table 4. Correlation matrix between variables.

	M-1 h	Sleep*	Epworth	Bioma**	FEV1/FVC	Educa	Age
M-1 h *p*-value	1						
Sleep* (Rho) *p*-value	-0.30 0.027	1					
Epworth (Rho) *p*-value	-0.41 0.002	**0.58** **<0.001**	1				
Bioma** *p*-value	0.04 0.817	0.17 0.281	0.22 0.174	1			
FEV1/FVC *p*-value	**0.61** **<0.001**	**-0.61** **<0.001**	**-0.60** **<0.001**	-0.18 0.271	1		
Educa *p*-value	-0.22 0.103	-0.01 0.937	-0.03 0.839	**-0.49** **0.001**	-0.07 0.613	1	
Age *p*-value	**-0.29** **0.035**	0.06 0.674	-0.06 0.659	-0.11 0.511	-0.14 0.333	-0.18 0.193	1

Educa: Education expressed as 0: null; 1: basic; 2: medium, 3: superior.

patients, so its exogenous administration has positive effects. It is known that the circadian sleep rhythm is closely related to the melatonin release rhythm [32-33], since melatonin is a hormone that regulates sleep in diurnal mammals, including humans. Sleep induction occurs shortly after the onset of endogenous melatonin release [34]. Its peak levels of secretion occur during the night at approximately 01:00 to 03:00h, with concentrations that can vary from 29.5 ± 2.2 to 37.6 ± 1 pg/ml in older patients depending on the study population [35-36]. Therefore, in this study, one of the objectives was the determination of nocturnal melatonin levels and the exploration of a correlation with poor sleep quality.

Interestingly, in this study the control group had melatonin values considered adequate for the age range of the participants, previously reported in a similar population of healthy patients [35]. The COPD group had low values compared to the control, similar results recently reported in blood samples in patients with acute exacerbation of COPD37. The nocturnal melatonin levels reported in this study could indicate that poor sleep quality in these patients could be influenced by the decreased values and altered melatonin release pattern. On the other hand, the loss of nocturnal melatonin release may be related to the chronicity of the disease and especially to the exposure of patients to light during the night when they present symptomatology38 and this becomes negative feedback on sleep quality, since melatonin is a hormone that is synthesized through a phototransduction process that is stimulated in the dark through the retina [39], therefore, exposure to artificial light during the night suppresses its secretion and decreases its release time in humans. However, one of the limitations of our study is that we did not measure the light intensity and exposure time of patients during the night, which would be important since light is the most important environmental signal for melatonin secretion.

Different studies have shown that exogenous melatonin administration improves sleep quality in COPD patients. However, the mechanisms have not been fully described, although two could be proposed. The first is due to the action melatonin has demonstrated in suppressing inflammatory cell infiltration in lung tissue [40], reducing lung destruction and necroptosis [37], as well as decreasing oxidative stress and dyspnea [41]. So far, most of the studies supporting these results have been performed in animal models, but they suggest limiting disease progression and reducing symptomatology in COPD patients, due to the decrease in airway inflammation, favoring a decrease in symptomatology and better sleep quality. Another mechanism would be regulated by the chronobiotic actions of melatonin on the circadian sleep-wake rhythm; if patients have low melatonin levels, they could recover adequate levels with exogenous administration of melatonin, which are required during the night to promote sleepiness and maintain sleep [42].

On the other hand, it has been widely studied that cortisol has a well-defined circadian rhythm. With high levels in the morning peaking at 60 minutes upon awakening, decreasing throughout the day, with low levels at dusk and during the night [43]. Cortisol is used as a phase marker of the circadian clock [44-45], therefore, in this study we measured cortisol to explore the possibility of a phase shift induced by exacerbation of nocturnal symptoms, exposure to light, and changes in melatonin secretion. Cortisol secretion is regulated by the hypothalamic-pituitary-adrenal axis (HPA) and melatonin has a regulatory effect on the HPA [46]. However, we found no significant differences between the groups. Both presented a daily pattern and normal cortisol values, even though melatonin levels are lower in the control group. Thus, our results indicate that low melatonin levels did not modify cortisol levels in the patients and agree with previous research in which no changes in cortisol level responding to light exposure have been reported [47].

Also, low values of the ratio of FEV_1/FVC indicate greater obstruction of the patient's airways [48]. This variable presented correlation with low nocturnal melatonin values, with sleep quality and with somnolence. This showed that the greater the airway obstruction, the lower the nocturnal melatonin, the worse the quality of sleep and the greater the daytime sleepiness. These results are like those reported in another investigation, where it was found that a lower FEV1 was accompanied by a higher PSQI score [29]. However, they differ from other authors who found no relationship of FEV_1 with sleep disturbances in COPD patients

[49-50].

In the present study we were able to characterize the importance of high exposure to smoke generated by biomass combustion; in rural regions of the state of Veracruz it is estimated that 25.2% of the population uses wood smoke as fuel for cooking with constant exposure to smoke [51-52]. This condition is mainly found in women who spend more time in this activity and are exposed to this pollutant. This is probably one of the reasons why the incidence of COPD in this study was higher in women. There are several studies that have established tobacco smoke as the main cause of COPD in the world [2, 53]. However, few studies have explored biomass exposure as a major factor in the development of COPD [16], although there are reports that around 3 billion people worldwide are exposed to biomass smoke [54], and it is estimated that almost 2 billion kg are burned every day to be used as an energy source for cooking or heating [55]. Therefore, future studies should address the issue of biomass exposure as a major factor in the development of COPD. Future studies should therefore address the risk of biomass exposure as a causal agent of COPD in developing countries, to implement strategies for its prevention and control.

CONCLUSION

With the results of this study we can conclude that patients with COPD should receive treatment to ensure that they have a good quality of sleep, therefore melatonin supplementation should be indicated in the treatment of these patients and not only the treatment of respiratory symptoms.

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