ORIGINAL ARTICLE

Diurnal and nocturnal serum melatonin concentrations after treatment with continuous positive airway pressure in patients with obstructive sleep apnea

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KEY WORDS

continuous positive airway pressure, melatonin, obesity, sleep-wake rhythm

ABSTRACT

INTRODUCTION Melatonin secretion, one of the main factors controlling the sleep-wake rhythm, may be disrupted in patients with sleep disorders.

OBJECTIVES The aim of the study was to evaluate the profile of circadian melatonin secretion in patients with obstructive sleep apnea (OSA) and to assess the impact of 2-day and 3-month treatment with continuous airway pressure (CPAP) on diurnal and nocturnal serum melatonin levels.

PATIENTS AND METHODS Serum melatonin levels were evaluated in 71 untreated patients with OSA and 18 healthy controls at 6 time points: 10 AM, 2 PM, 6 PM, 10 PM, 2 AM, and 6 AM. The measurements were repeated after 2 days and 3 months of CPAP treatment.

RESULTS Melatonin secretion rhythm was altered in 25.4% of the patients with OSA. In patients with preserved secretion rhythm, the serum melatonin level was significantly lower at 2 AM and 6 AM, compared with healthy controls: 68.2 pg/ml (interquartile range [IQR], 30.1–109.8 pg/ml) vs 109.1 pg/ml (IQR, 63–167.9 pg/ml), $P = 0.02$ and 40.8 pg/ml (IQR, 20.8–73.2 pg/ml) vs 67.7 pg/ml (IQR, 32.7–131.7 pg/ml), $P = 0.04$, respectively. Melatonin levels did not change significantly after the 2-day and 3-month CPAP treatment. However, at 3 months, a shift of the peak melatonin concentration to 2 AM was observed in patients with an altered secretion rhythm.

CONCLUSIONS OSA has a significant effect on serum melatonin levels. Neither short-term nor long-term CPAP treatment significantly changes melatonin concentrations; however, our results seem to indicate that a 3-month CPAP treatment may be helpful in restoring the physiological rhythm of melatonin secretion in patients with OSA.

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INTRODUCTION Melatonin is a serotonin-derived hormone secreted by the pineal gland in a cyclic manner.[1] It has diverse activities and regulates numerous physiological processes in mammals, including the sleep-wake rhythm, sexual maturation, reproduction, and aging. It also has antioxidant, oncostatic, and immunomodulative properties.[1-3] Its release responds to the light-dark cycle.[4-6] The peak melatonin secretion occurs during the night hours; during the day, its concentrations are low. Exposure to light acutely suppresses nocturnal melatonin release.[7-9] Studies in animal models and humans have shown that melatonin secretion is strongly related to sleep, and individuals with decreased melatonin levels suffer from sleep disturbances and insomnia. This refers to elderly patients (as melatonin concentrations tend to fall with age), night-shift workers with an exogenously disrupted sleep-wake rhythm, individuals who had undergone pinealectomy, and others.[1,2,10] In patients with primary insomnia, exogenous melatonin decreases sleep onset latency, increases total sleep time, and improves sleep quality.[11,12] Melatonin also effectively reduces jet

lag symptoms and sleep disorders related with night-shift work.[13,14]

Obstructive sleep apnea (OSA) is a common condition characterized by recurrent airflow limitation in the upper airways, leading to a decrease in blood oxygenation and subsequent arousals. The prevalence of OSA depends on age and sex, among other factors, and is estimated at 13% in men and 6% in women aged 30 to 70 years; it has shown a relative percentage increase by 14% to 55% over the last 20 years.[15] OSA is associated with significant comorbidity and is an important risk factor for diabetes and cardiovascular diseases.[16,17] It is currently regarded as one of the most frequent causes of arterial hypertension and is the most common comorbidity in patients with arterial hypertension resistant to treatment.[18,19]

Recurrent fits of apnea/hypopnea and awakenings, which are typical for OSA, result in sleep fragmentation and a reduction in sleep duration and quality. It is likely that sleep disorders in these patients may cause disturbances in melatonin secretion. Assuming also that continuous positive airway pressure (CPAP) treatment reduces or even eliminates abnormal breathing during sleep and restores the physiological sleep structure,[20] the question arises whether this form of treatment may have an impact on melatonin secretion. Only a few studies attempting to establish the relation between OSA and circadian secretion of melatonin have been published to date.[21-24] The majority of them have been conducted in small groups of patients and used varying study protocols. There were substantial differences in the tools used for OSA diagnosis and the time of serum melatonin measurements, with melatonin evaluation only at night in some reports[21,22,24] and only in the afternoon in others.[23] Therefore, we undertook a study with the aim to evaluate the profile of circadian melatonin secretion in patients with OSA and to assess the impact of a 2-day and 3-month treatment with CPAP on melatonin circadian rhythm.

PATIENTS AND METHODS

Study design Study participants were recruited from patients referred to the Sleep Laboratory of the Department of Internal Medicine, Pulmonary Diseases and Allergy of the Medical University of Warsaw, Warsaw, Poland, between the years 2007 and 2012, due to excessive daytime drowsiness, loud snoring, or apneas observed during sleep. All patients underwent polysomnography (PSG) and serial measurements of the serum melatonin level (every 4 hours including nighttime during diagnostic PSG). The cohort was subsequently divided into 2 groups: patients in whom PSG confirmed the diagnosis of OSA and those in whom PSG excluded the disease (control group). Patients with OSA received CPAP treatment, and serum melatonin levels were assessed after 2 days. Patients were then scheduled for a follow-up visit after 3 months. During the follow-up visit, adherence to CPAP treatment was assessed, and serial measurements of serum melatonin concentrations were repeated.

The study was approved by an institutional review board. Informed consent to participate in the study was obtained from all participants.

Study participants A total of 108 consecutive patients were enrolled to the study. Among them, OSA was confirmed in 90 patients. The diagnosis of OSA and its severity were established in accordance with the recommendations of the American Academy of Sleep Medicine.[25] The diagnostic criteria were as follows: apnea–hypopnea index (AHI) of 5/h or higher in the presence of typical OSA symptoms or AHI exceeding 15/h regardless of the clinical manifestation. The diagnosis of OSA and an AHI exceeding 15/h and consent to CPAP treatment were the 2 inclusion criteria for further analyses. The exclusion criteria were as follows: shift work; current or past disease of the central nervous system (history of stroke, epilepsy, tumors, previous neurosurgical intervention); current or past endocrine dysfunction (eg, hypothyroidism or hyperthyroidism, disorders of the pituitary gland or adrenal glands); chronic kidney or liver diseases; mental illness (current or past); lack of consent to CPAP treatment; no indications for or contraindications to CPAP treatment; and selection of an alternative method of treatment by the patient.

The control group comprised of individuals in whom PSG did not confirm the diagnosis of OSA. For this group, the same exclusion criteria were applied (except the issues associated with OSA treatment).

In all participants, clinical and anthropometric data were recorded. Sleepiness was assessed by the Epworth Sleepiness Scale (ESS).[26]

Polysomnography PSG was conducted with an Alice 4 camera (RESPIRONICS, Murrysville, Pennsylvania, United States) in an acoustically isolated room. The test was supervised by a respiratory physician or by a trained technician. The monitoring started at 11 PM and was terminated at 6 AM the next morning. Airflow was registered with a nasal cannula and thermistor. Movements of the chest and abdomen were monitored by inductive plethysmography. The body position was recorded with a gravity sensor. Arterial oxygen saturation was measured with pulse oximetry at the fingertip. The structure of sleep was assessed based on the records of electroencephalogram, electrooculogram, and electromyogram. An electrocardiogram was also recorded. During PSG, patients were continuously monitored by a video camera. Sleep structure was assessed according to the guidelines of Rechtschaffen and Kales.[27]

Treatment with continuous positive airway pressure The criteria for CPAP treatment were based on the recommendations of the American Thoracic Society.[28] During the first 2 nights of hospital treatment, all 71 patients with indications

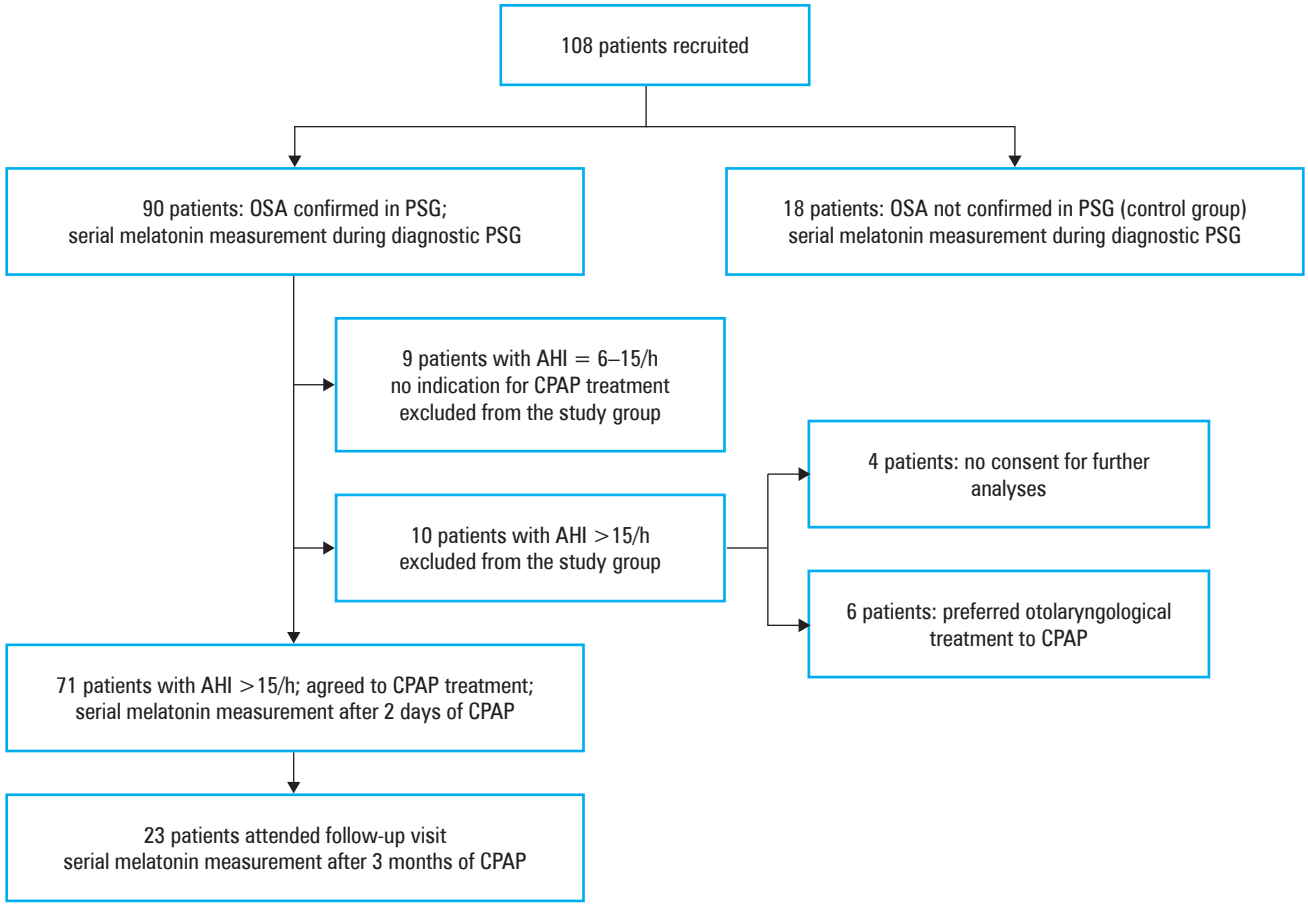

FIGURE 1 Study flowchart
Abbreviations: CPAP, continuous positive airway pressure; ORL, otolaryngology; OSA, obstructive sleep apnea; PSG, polysomnography

for CPAP treatment used an autoCPAP (S8 Autospirit ResMed, Abingdon, United Kingdom). After discharge, 56 patients bought their own CPAP (with partial reimbursement from the Polish National Health Fund) and 15 patients decided to rent the device. The type of the device used for further treatment depended on the patients' own choice and economic factors. Treatment adherence was evaluated on the basis of the data saved in the memory system of the CPAP device. Only patients using CPAP for at least 4 hours per night were included in the final analysis.

Serum melatonin level measurements Serum melatonin levels were determined using a radioimmunoassay (Melatonin RIA-0355 kit, DRG, Marburg, Germany). The measurements were performed at 6 time points: 10 AM, 2 PM, 6 PM, 10 PM, 2 AM, and 6 AM. To minimize unpleasant sensations associated with frequent blood sampling, nocturnal blood was drawn through a peripheral intravenous cannula placed in the basilic or cephalic vein. If light was required during blood sampling at night, its intensity was less than 40 lux. The samples were immediately frozen and stored at –70°C until analysis. The measurements were performed in thawed serum according to the manufacturer's instructions.[29]

Serial serum melatonin concentrations were assessed at baseline in all participants. The measurements were repeated in patients with OSA after 2 days and 3 months of the CPAP treatment.

Statistical analysis Statistical anlysis was performed using Statistica 8.0 (StatSoft Inc., Tulsa, Oklahoma, United States). Data were expressed as medians and interquartile ranges (IQRs). For nonnormally distributed parameters, the differences between continuous variables in the groups were tested using the nonparametric Mann–Whitney test. The χ^2 test was used to analyze categorical variables in different groups. Related variables were compared using the Wilcoxon test for paired observations (serum melatonin concentrations before and after treatment), while Friedman test, for the comparison of multiple (>2) measurements of the same variable. A P value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the patients A total of 108 consecutive patients (66 men and 5 women; mean [SD] age, 49.2 [9.1] years) were enrolled to the study. PSG confirmed the diagnosis of OSA in 90 patients, of whom 19 were excluded from further analyses (FIGURE 1). The control group comprised 18 participants in whom OSA was excluded by PSG. The characteristics of patients are presented in TABLE 1.

The study groups did not differ significantly in terms of smoking history, alcohol consumption, diet, or physical activity. Patients with OSA had a higher incidence of arterial hypertension and diabetes than controls (63.4% vs 27.8%, $P = 0.006$ and 21.1% vs 0%, $P = 0.03$, respectively).

TABLE 1 Clinical characteristics of the study groups

Parameter	Patients with OSA (n = 71)	Control group (n = 18)	*P* value[a]
Age, y	49.2 (36–62.5)	44.6 (30.1–66)	0.03
Men/women, n (%)	66 (93)/5 (7)	17 (94)/1 (6)	NS
BMI, kg/m^2	31.7 (27–36.3)	29.6 (25.3–32.1)	0.01
Neck circumference, cm	45 (40–48)	44 (41–45)	0.04
Systolic blood pressure, mm Hg	130 (118–145.3)	127.5 (116–136.2)	NS
Diastolic blood pressure, mm Hg	80 (74.3–89)	77.5 (74.3–84.1)	NS
Daytime PaO_2, mm Hg	78.3 (65.2–86.1)	85.5 (75.3–88)	0.04
Daytime $PaCO_2$, mm Hg	40.2 (35.6–49.9)	41.6 (35.1–46)	NS
ESS score, points	13 (8–20)	7 (5–13)	0.002
AHI, hour^{-1}	40.1 (18.3–87.1)	2.3 (0.8–4.5)	0.0001
DI, hour^{-1}	39 (17.7–76)	2.0 (1.1–4.2)	0.0001
Mean SpO_2 during sleep, %	93 (88.4–95)	94.8 (92.3–95)	0.002
Minimum SpO_2 during sleep, %	79.2 (60.8–89.2)	88.5 (86–92.3)	0.0001

Data are presented as median and interquartile range unless otherwise stated.

a Mann–Whitney test

Abbreviations: BMI, body mass index; ESS, Epworth Sleepiness Scale; AHI, apnea–hypopnea index; DI, desaturation index; NS, nonsignificant; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; SpO_2, blood oxygenation (transcutaneous pulse oximetry)

Baseline serum melatonin concentrations In the majority of the study population, the highest serum melatonin levels were noted at 2 AM (FIGURE 2). This finding was reported for all controls and for 53 of the 71 patients (74.6%) with OSA. However, the serum melatonin levels were lower in patients with OSA than in controls, both at 2 AM (median [IQR], 68.2 pg/ml [30.1–109.8 pg/ml] vs 109.1 pg/ml [63–167.9 pg/ml], respectively, $P = 0.02$) and at 6 AM (median [IQR], 40.8 pg/ml [20.8–73.2 pg/ml] vs 67.7 pg/ml [32.7–131.7 pg/ml], respectively, $P = 0.04$).

The melatonin secretion rhythm was altered in 18 patients (25.4%) with OSA; its level peaked at 6.00 AM in 10 patients (14%), at 10.00 PM in 7 patients (10%), and at 6 PM in 1 patient (1%). These patients did not differ in terms of the anthropometric data, arterial blood oxygenation, or OSA severity from those in whom the secretion rhythm was preserved.

No correlations were found between serum melatonin concentrations at any time point and AHI or the ESS score. A trend towards lower melatonin levels at 2 AM and higher melatonin levels at 2 PM and 6 PM with increasing OSA severity was noted, but the differences between serum melatonin levels at those time points in patients stratified according to the AHI (5–14/h, 15–29/h, and ≥30/h) did not reach significance.

Serum melatonin concentrations in patients with sleep obstructive apnea before and after treatment with continuous positive airway pressure In all 71 patients with OSA, the treatment goal, that is, the AHI of less than 5/h, was achieved during the first 2 days of CPAP treatment. There were no differences in serum melatonin levels in patients at any of the time points after short-term CPAP use.

At 3 months, data were available only for 23 patients with OSA (32%, only men); 48 patients were lost to follow-up: 18 patients discontinued the treatment due to side effects (11 patients, mask intolerance; 4, chronic rhinitis; 3, dryness of the mouth), and 11 patients who initially rented the device discontinued the treatment due to economic reasons. Twelve patients preferred otolaryngological treatment. Seven patients withdrew their consent for rehospitalization. Of the 23 participants who attended the follow-up visit (24-hour hospitalization with control PSG and repeated blood sampling), 11 patients used an auto-CPAP (Good Knight 420E, Tyco Healthcare, Tullamore, Ireland; Puritan Bennett, Nancy, France; REMstar auto, RESPIRONICS; S8 Autospirit ResMed) and 12 used a standard CPAP device (Good Knight E, Tyco Healthcare; Puritan Bennett; HC 600, Fisher&Pykel, Auckland, New Zealand; S8 Escape, ResMed).

All patients had been using CPAP for more than 4 hours per night. The median (IQR) duration of CPAP use was 97 days (92.3–101 days) and 5.8 hours/night (5.1–6.5 hours/night). The median (IQR) pressure applied was 10 cmH_2O (8.21–13.1 cmH_2O). In all patients, an AHI of less than 5/h was achieved. The CPAP treatment also resulted in a reduction in daytime sleepiness (median [IQR] ESS score, 13 [8–20] vs 8 [6.2–9.1], respectively, $P = 0.0008$), lower systolic blood pressure (median [IQR], 130 mm Hg [118–145.3 mm Hg] vs 120 mm Hg [117.3–129 mm Hg], $P = 0.001$) and a lower heart rate (median [IQR], 75 bpm [71.7–82.3 bpm] vs 70 bpm [62.3–80.1 bpm], $P = 0.009$).

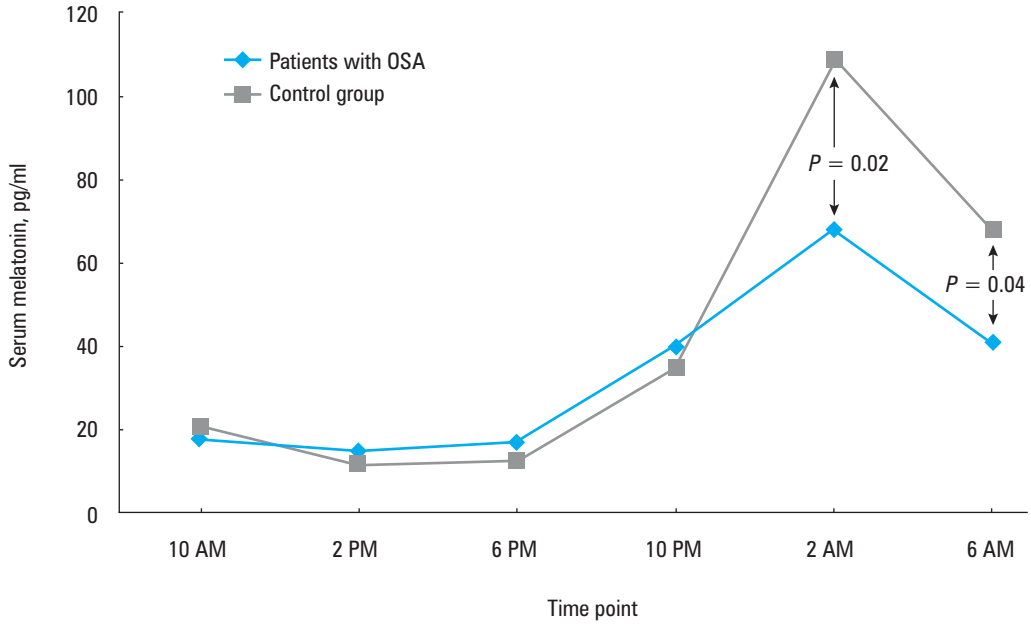

FIGURE 2 Baseline serum melatonin concentrations in patients with obstructive sleep apnea (OSA) and healthy controls at the selected time points

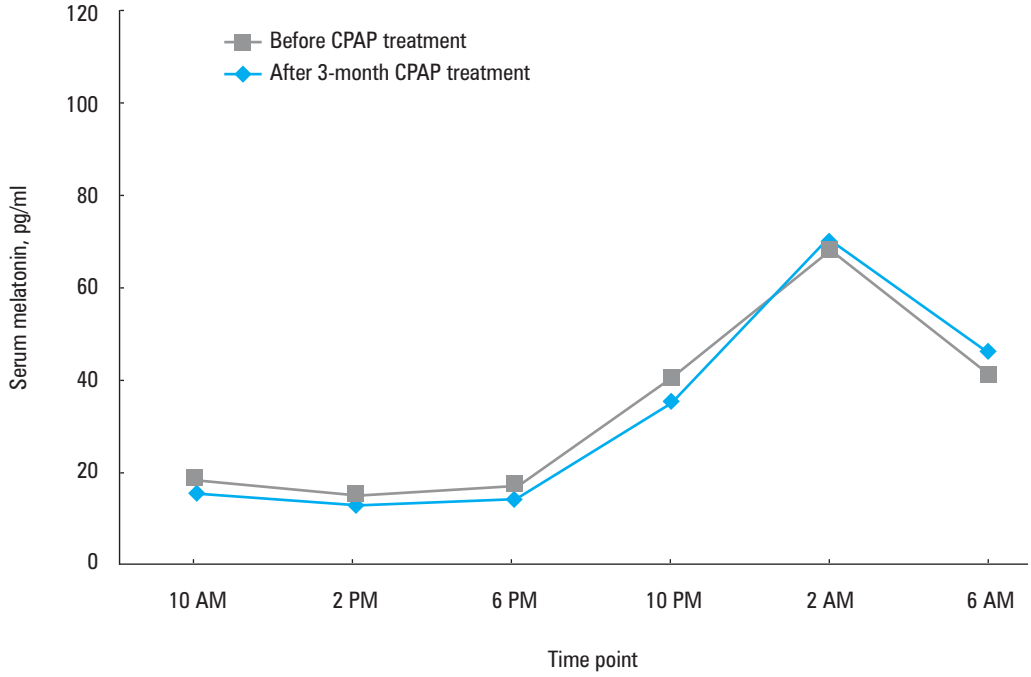

FIGURE 3 Serum melatonin levels at the selected time points in patients with obstructive sleep apnea (OSA) before and after 3 months of treatment with continuous positive airway pressure (CPAP)

The 3-month CPAP treatment did not have a significant impact on serum melatonin levels at any of the time points (FIGURE 3). However, in 5 of the 6 patients whose melatonin concentration had peaked at a time point other than 2 AM, a shift to 2 AM after the CPAP treatment was observed. This included 3 patients in whom pretreatment peak melatonin levels were noted at 6 AM and 2 patients in whom the highest concentration of melatonin before treatment was observed at 10 PM.

DISCUSSION The present study demonstrated that up to 25% of patients with OSA have an altered circadian pattern of melatonin secretion, with a shift of its peak concentration to a different time point than in the physiological rhythm. Importantly, although serum melatonin levels did not change significantly after 3 months of CPAP treatment, in 5 out of 6 patients whose melatonin concentration had peaked at a time point other than 2 AM, a shift towards the maximum melatonin concentration at 2 AM was observed. Furthermore, we demonstrated that in patients with OSA who have a preserved circadian rhythm of melatonin secretion, serum melatonin levels are significantly lower at 2 AM and 6 AM when compared with healthy controls. This confirms the impact of OSA-related sleep disturbances on melatonin secretion. Unlike the majority of previous studies that applied only screening methods for the diagnosis of OSA, our study was conducted in a well-defined group of patients with OSA confirmed by PSG. Also, to our knowledge, this is the

first study assessing serum melatonin levels both during the day and at night, while the previous studies evaluated either only nocturnal or only diurnal melatonin concentrations. Furthermore, this is probably the first study to assess the impact of long-term treatment with CPAP on melatonin secretion in patients with OSA.

Our results are similar to the those of Brzecka et al.[22] The authors found a preserved circadian melatonin secretion rhythm in 67% of the patients with OSA; in 27%, there was a shift of peak melatonin levels towards the morning hours, and in 6%, towards the evening hours. Surprisingly, however, patients with higher melatonin levels at 2 AM had more severe OSA.[22] This is in contrast to our results because, in general, melatonin levels at nighttime were lower in patients than in controls in our study, and we found no correlation between serum melatonin levels and severity of OSA. Hernandez et al[24] also found a shift of the maximum serum melatonin concentrations to 6 AM in their cohort of 20 patients with OSA. However, in one of the first studies on melatonin in OSA, Wikner et al,[21] who studied only nocturnal melatonin concentrations, demonstrated that in patients with OSA neither the rhythm of melatonin secretion nor serum melatonin levels at particular time points differed significantly from those in healthy individuals. These authors used night pulse oximetry as the diagnostic criterion for OSA, so their results must be interpreted with caution, as they apply to patients with oxygen desaturation at night regardless of the underlying cause.

The mechanism leading to alterations in melatonin secretion in the course of OSA has not been fully elucidated. Moreover, it is not clear whether melatonin secretion disturbances in OSA are a causal factor or, more probably, a phenomenon secondary to the disease. Recurrent apnea and related nocturnal hypoxemia may affect the function of the pineal gland. Disruption in melatonin secretion has been reported in individuals with an altered day-night rhythm, including night-shift workers, travelers changing time zones, and subjects kept in an illuminated environment.[13,14] It has been documented that light and darkness influence the synthesis and release of melatonin by indirect activation (darkness) and inhibition (light) of arylalkylamine N-acetyltransferase and hydroxyindole-O-methyltransferase, 2 enzymes that catalyze melatonin production from serotonin.[1] An altered sleep-wake rhythm and associated prolonged exposure to light may therefore contribute to lower serum melatonin concentrations in patients with sleep disorders by reducing its synthesis from serotonin. However, studies on this topic in OSA are lacking.

Decreased melatonin production may increase the risk of obesity by inducing insulin resistance, glucose intolerance, and alterations in the circadian metabolic rhythm.[30] Wetterberg et al[9] showed that melatonin levels are inversely correlated with body mass. Both features, that is, an altered day-night rhythm due to sleep disturbances and obesity, are hallmarks of OSA. Nevertheless, we did not find correlations between serum melatonin and body mass index in our patients.

Melatonin concentrations also depend on the duration of sleep.[4,5] This might explain the differences in melatonin concentrations among studies that applied the same method for serum melatonin analysis. The values reported by Hernandez et al[24] were lower than those in our study, but also the total sleep time of the patients was shorter than that in our study (mean [SD], 274 [61] min vs 343 [57] min, respectively). At the same time, the basic patient characteristics (age, body mass index, AHI, and ESS score) were similar in both studies.

Besides the reduction of body weight, treatment with CPAP remains the cornerstone in the therapy of OSA.[31,32] However, the effects of CPAP on OSA have been evaluated at various time intervals from treatment onset and depend on study endpoints. Earlier studies have shown that a 3-month use of CPAP in patients with OSA decreased serum lipid concentrations[33] and might affect cardiac remodeling, which is altered in the course of the disease.[34,35] Hernandez et al[24] demonstrated that positive effects of CPAP treatment on the melatonin concentration defined as shift of the peak serum melatonin level from 6 AM to 2 AM can be seen as early as on the first day of CPAP use. We did not find significant differences between serum melatonin concentrations at any of the analyzed time points after 2 days of treatment with CPAP. Although we also failed to find significant differences in melatonin levels after 3 months of CPAP use, we noted a shift of peak concentrations to 2 AM in 5 of the 6 patients with initially altered melatonin secretion rhythm who attended the follow-up visit. We are unable to discuss our results in comparison with the results of other authors because data on the impact of long-term CPAP treatment on melatonin secretion in patients with OSA are lacking. Wikner et al[21] did not find significant differences in serum and urine melatonin levels after a 4-week CPAP treatment; however, this study had some methodological limitations as described by the authors, and the treatment period was much shorter than that analyzed in our study.

The small number of patients who had completed the study protocol is the major limitation of our study. They accounted for 32.4% of the initially enrolled patients. This is a common problem in studies that are designed to evaluate the long-term effect of CPAP treatment. The control of CPAP use after 2 days was possible in the whole group because the treatment was initiated during the hospital stay with a device that did not belong to the patient. On discharge, a recommendation of CPAP purchase was given; however, we were not able to assess the number of patients who decided to continue this treatment because they were lost to follow-up. It is estimated that from 50% to 80% of patients with OSA

discontinue CPAP therapy, and the proportion of patients who use CPAP for at least 4 hours during sleep only slightly exceeds 40%.[31,36] The control visit also required hospitalization (1 day), which may have been discouraging for professionally active patients, who comprised the majority of our group. Furthermore, we may speculate that the small number of patients may have been a result of the requirement of repeated blood sampling. The fact that the effect of 3-month CPAP use was evaluated only in men is another limitation of this study. However, there was a marked male predominance among the patients recruited to the study (93% vs 7%), which was to be expected considering the epidemiology of OSA in Poland[37] and worldwide.[15] The studies by Wikner et al[21] and Brzecka et al[22] included only men.

The use of serum melatonin concentrations may also be considered a limitation. Serum melatonin concentrations are relatively variable,[38] and the measurement of its stable metabolite, 6-sulfatoxymelatonin, in urine has been applied in a number of studies to better reflect melatonin secretion.[39,40] In a recent study, Reutrakul et al[40] showed that OSA severity was associated with lower melatonin secretion evaluated indirectly as a lower urinary 6-sulfatoxymelatonin-to-creatinine ratio.[40] However, our study was aimed at the assessment of melatonin secretion rhythm, which required serial measurements. Serial urine sampling (particularly at night) would have caused significant technical problems; furthermore, a comparative analysis of the obtained results would be impossible, as most of the studies involved 6-sulfatoxymelatonin measurement in the overnight or cicardian urine collection.

To conclude, OSA has a significant impact on serum melatonin levels. Approximately 25% of patients with OSA have an altered circadian rhythm of melatonin secretion. In OSA patients with a preserved secretion rhythm, peak melatonin levels at night are significantly lower than those in healthy subjects. Neither short-term (2-day) nor long-term (3-month) treatment with CPAP significantly changed melatonin levels; however, our results seem to indicate that a 3-month period of CPAP treatment may be helpful in restoring the physiological rhythm of melatonin in patients with OSA with a disrupted secretion profile.

Contribution statement MB, PB, and RCh designed the study. MB, MM-W, PB, and MK were responsible for literature search, patient recruitment, and data analysis. MB and MM-W prepared the first draft. All authors critically reviewed the manuscript and contributed to the final version.

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