Original Article

Causes of sleep disturbance in human immunodeficiency virus-infected individuals

Is it depression or obstructive sleep apnea?

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ABSTRACT

الأهداف: فحص العلاقة المحتملة بين انقطاع النفس الانسدادي النومي والاكتئاب على جودة النوم لدى الأشخاص المصابين بفيروس نقص المناعة البشرية (PWLHIV) .

المنهجية: تم تضمين البالغين PWLHIV في هذه الدراسة المستعرضة المحتملين ، دراسة الحالات والشواهد . اكتملت الدراسة على 99 مريضًا و 80 شخصًا من المجموعة الضابطة . للتحقق من جودة النوم ، تم استخدام مقياس جودة النوم في بيتسبرغ ومقياس ستانفورد للنوم . لتحديد مخاطر OSA، تم استخدام استبيانات برلين و STOP–BANG ؛ ولتقييم وجود ودرجة الاكتئاب ، تم تطبيق قائمة Beck Depression Inventory .

النتائج: كان لدى المرضى نعاس أعلى بشكل ملحوظ أثناء النهار (p=0.002) وغياب الذهن (p=0.004) . كان معدل القدرة على التركيز على عمل الفرد أعلى بشكل ملحوظ في المجموعة الضابطة مقارنة بمجموعة المرضى (p=0.000) . كان المزيد من المشاركين في مجموعة المرضى يعانون من ضعف جودة النوم (57%مقابل 47.5%) . كانت درجة جودة النوم أعلى بشكل ملحوظ في مجموعة المرضى (5.23 مقابل 6.32 ؛p=0.032) . كان الخلل الوظيفي أثناء النهار أعلى بكثير في مجموعة المرضى (p=0.004) . كان معدل خطر انقطاع النفس الانسداد النومي متشابهًا بين مجموعة المرضى والمجموعة الضابطة في كل من استبيانات برلين و STOP–BANG p=0.443 و p=0.581 . كانت معدلات وأعداد الاكتئاب في مجموعة المرضى أعلى بشكل ملحوظ (p=0.007) .

الخلاصة: تشير النتائج إلى أن الاكتئاب قد يكون السبب الأكثر احتمالا لاضطرابات النوم لدى الأشخاص المصابين بفيروس نقص المناعة البشرية، بغض النظر عن انقطاع التنفس أثناء النوم .

Objectives: To examine the possible associaton of obstructive sleep apnea (OSA) and depression on sleep quality in people living with human immunodeficiency virus (PWLHIV).

Methods: Adult PWLHIV were included in this prospective, cross-sectional, case-control study. Our study was completed with 99 patients and 80 control subjects. To investigate sleep quality, the Pittsburgh Sleep Quality Scale and Stanford Sleepiness Scale were used; to determine the risk of OSA, the Berlin and STOP-BANG questionnaires were used; and to evaluate the existence and degree of depression, the Beck Depression Inventory was applied.

Results: Patients had significantly higher daytime sleepiness (p=0.002) and absent-mindedness (p=0.004). The rate of being able to concentrate on one's work was significantly higher in the control group compared with the patient group (p=0.000). More participants in the patient group had poor sleep quality (57% versus [vs.] 47.5%). The sleep quality score was significantly higher in the patient group (6.32 vs 5.23; p=0.032). Daytime dysfunction was significantly higher in the patient group (p=0.004). The rate of OSA risk was similar between the patient group and the control group on both the Berlin and STOP-BANG questionnaires (p=0.443 and p=0.581). Rates and numbers of depression the patient group were significantly higher (p=0.007).

Conclusion: The results suggest that depression may be the most likely cause of sleep disorders in PWLHIV, regardless of OSA.

Keywords: depression, HIV, obstructive sleep apnea, sleep disorders, sleep disturbance

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Human immunodeficiency virus (HIV) infection has become a chronic disease, and people live almost all of their lives with HIV. In addition, antiretroviral treatment (ART) has decreased the mortality and morbidity due to HIV-induced acquired immunodeficiency syndrome (AIDS).[1] The transition from HIV infection to chronic disease with effective/intensive antiviral use even reduces the long-term impact of the disease more important.[2,3] Therefore, sleep disorders increase in patients infected with HIV.[4] It is estimated that approximately 73% of people living with HIV experience at least one daily symptom, such as restlessness, nervousness or daytime sleepiness, with symptoms of insomnia.[3]

However, in many recent case-referent studies, obstructive sleep apnea (OSA), diabetes, cardiovascular disease, direct effects of HIV on the central nervous system, compromise of the immune system, side effects of some ART regimens (especially use of an ART regimen with efavirenz [EFV]).[3,5] Drug abuse and depression have been shown to cause sleep disturbances in individuals living with HIV.[2] In another study, Voss et al[6] up to 50% of people with HIV infection have sleep problems, although the causes of such problems have not been adequately researched or treated. Causes of sleep problems in patients infected with HIV are not yet fully understood. In this study, we aimed to evaluate whether sleep disorder exists in these patients, and whether sleep is affected from OSA or depression.

Methods. In this prospective, cross-sectional data analysis, HIV-infected persons aged 18 years and older, applied to the Department of Infectious Diseases outpatient clinic, Gaziantep University Medicine Faculty Hospital, Gaziantep, Turkey between April and July 2019, were included. Demographic data, including patient age, gender, occupation, and past and current comorbidities of the patients, were collected from participants' personal records and hospital records were reviewed. Written informed consent of both patients and control groups were obtain.

The presence of pain in the one month before enrollment and during of the study was recorded. Patients who described pain, diagnosed psychiatric and neurological disorders were excluded from the study due to effects of sleep quality on them. People working night shifts were not included in the study, because such work patterns may affect sleep quality. Patients on EFV (Sitocrin®) therapy was also excluded because of their known effects on the central nervous system.[3,7]

The Pittsburgh sleep quality scale (PSQI) and Stanford Sleepiness Scale were used to evaluate sleep quality. Firstly, the PSQI is a questionnaire that has been developed on the 1989. It includes 19 questions and allows to evaluate subjective sleep quality over the previous month. The questions are divided into 7 different categories, and each category is weighted equally from 0-3. Once all the questions are answered, the scores from each category are added together to create a global score. This score can range from 0-21, with higher scores indicating poorer sleep quality.[8] A total score of 5 or above on the PSQI, which evaluates 7 components classified as sleep disturbances; latency, efficiency, duration and quality of sleep, need for medication and loss of daytime function, and indicates poor sleep quality (90% sensitivity, 87% specificity).[2,9,10] In our study, the Turkish version of the questionnaires included in the OSA syndrome diagnosis and treatment consensus report prepared by the Turkish Thoracic Society was used.

The Stanford sleepiness scale (SSS) is used to determine the level of daytime sleepiness; it is a subjective questionnaire. The questionnaire contains 7 statements; i) Feeling active and constantly alert, ii) Functions are high but not maximal, can concentrate on work iii) Awake but relaxed, responding but fully not alert, iv) sometimes absent-minded, v) Confused and slowed in movements, vi) There is a pronounced feeling of drowsiness, always prefers to lie down, and vii) Cannot stay awake, falls asleep soon, always like in a dream. Daytime sleepiness is graded as 1 for the mildest and 7 for the most severe sleepiness.[10,11] In our study, the Turkish version of the SSS included in the OSA syndrome diagnosis and treatment consensus report prepared by the Turkish Thoracic Society was used.

Assessment of the risk of OSA syndrome: Numerous questionnaires are available for identifying high risk of OSA. The Berlin survey is one of these surveys. Berlin and STOP-BANG questionnaires were used to determine the risk of OSA. The Berlin questionnaire, which was also used in our study, consists of 3 categories and 10 questions. Category 1 includes 5 questions on snoring, category 2 includes 3 questions on daily sleep and category 3 includes 2 questions on the presence of hypertension and a body mass index (BMI) of 30 kg/m^2 or more. On the questionnaire, positive results in 2 or more categories from the survey responses show that the risk of OSA is high in the respondent; if there is

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a positive result in only one category or no positive result, it shows that the risk of OSA is low.[5,10,12,13] In our study, the Turkish version of the Berlin questionnaire included in the OSA syndrome diagnosis and treatment consensus report prepared by the Turkish Thoracic Society was used.

Another questionnaire used to evaluate the potential of individuals for OSA is the STOP-BANG Questionnaire. This questionnaire has 2 components. STOP questions and evaluation: S-Snore (do you have loud snoring?), T-Tired (are you tired and sleepy during the day?), O-Observed (has anyone ever said that your breathing stops during sleep?), P-Pressure (have you used medication because of high blood pressure?). Second component's questions are B-BMI (body mass index >35 kg/m^2), A-Age (age >50), N-neck (neck circumference > 40 cm), G-Gender (male gender). The yes answer to each question is evaluated as 1 point. In this instrument, a score of 0–2 is considered to represent low risk, 3-4 to represent medium risk, and 5-8 to represent high risk.[2,10,14] In our study, the Turkish version of the STOP-BANG included in the OSA syndrome diagnosis and treatment consensus report prepared by the Turkish Thoracic Society was used.

The Beck Depression Inventory (BDI) was used to evaluate the presence and severity of depression. The BDI consists of 21 questions, and each question includes symptoms that are rated from 0 (absence of depressive symptoms) to 3 (presence of severe symptoms). Accordingly, after evaluation, the total BDI score will be between 0 and 63 points. Rating of the inventory is classified as minimal depression: 0-13 points, mild depression: 14-19 points, moderate depression: 20-28 poinst and severe depression: 29-63 points.[15,16] In our study, we used Turkish version of the BDI.

Statistical analysis. Results were presented as mean and ± standard deviation (SD) for continuous variables, frequency and percentages for categorical variables. Data normality were tested by Shapiro-Wilk test for continuous variables. Comparisons among the study groups were performed using parametric [t test] and non-parametric [Mann Whitney U test] tests depending on data normality. The relationship between categorical variables were tested by Chi-square test. A *p*-value <0.05 was considered statistically significant. IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA was used for the statistical analysis). We estimated, the PSQI and BDI show good reliability and validity, with Cronbach's α coefficients of 0.88 and 0.82.

The study was approved by Gaziantep University Clinical Research Ethics Committee (Decion No:2019-268, dated 19.06.2019). All procedures conducted in studies involving human participants comply with the ethical standards of the Gaziantep University Clinical Research Ethics Committee and the 1964 Declaration of Helsinki and any subsequent amendments or standards.

Results. During the study period, 381 patients were evaluated for the feasibility of the questionnaires. A total of 122 patients who accept to contribute were enrolled to our study. During the questionnaire administration, 23 patients decided to withdraw from the study. The study was completed with 99 patients and 80 control subjects with similar characteristics.

The study included 179 volunteers, with 99 HIV-infected patients, and 80 HIV-uninfected control subjects. Table 1, shows age of the patients, gender, marriage rate, neck circumference and BMI were not statistically different in both groups.

Stanford sleepiness scale. Patients had significantly higher daytime sleepiness (p=0.002) and absentmindedness (p=0.004) than the controls. The rate of being able to concentrate on work was higher in the controls (p=0.000). The detailed findings of Stanford Sleepiness Scale analysis are presented in Table 2.

Pittsburgh sleep quality scale. Estimated total score of applied Pittsburgh Sleep Quality Scale was >5 in both groups. However, the number of people with poor sleep quality was numerically higher in the patient group (57% vs 47.5%). Moreover, when the mean scores were compared, the sleep quality score was significantly higher in the patient group (p=0.031) (Table 3).

Each component of the Pittsburgh Sleep Quality Scale was evaluated separately results are presented in Table 3. Only in the 7th component (daytime dysfunction), was significantly higher in the patients (p=0.004).

Berlin questionnaire. Berlin questionnaire, used to calculate OSA risk, is divided into three categories. Patients with significant scores in ≥2 categories are considered high risk. The detailed findings of all three

Table 1 - Comparison of demographic characteristics of people living with human immunodeficiency virus and healthy controls

Parameters	Patient (n=99)	Control (n=80)	*P*-value
Age (Years)	39±10.2	35.8±14.5	0.071
>50 years, n(%)	12 (12.1)	16 (20.0)	0.217
Married, n(%)	33 (48.5)	30 (37.5)	0.244
Male gender, n(%)	87 (87.9)	65 (81.3)	0.307
Body mass index (kg/m^2)	25.7±4.6	25.6±4.3	0.913
Neck circumference (cm)	39.4±2.4	39.9±3.9	0.548

Table 2 - Findings of sleep quality obtained by using Stanford Sleepiness Scale in people living with human immunodeficiency virus and healthy controls.

Sleepness state	Patient n (%)	Control n (%)	*P*-value
Feeling active and constantly awake	27 (27.3)	17 (21.3)	0.450
Functions at a high level but not maximum, able to concentrate on work	22 (22.3)	45 (67)	<0.001
Awake but relaxed, responsive but not fully alert	7 (7.1)	11 (13.8)	0.220
Sometimes absent-minded	19 (19.2)	3 (3.8)	0.004
Absent-minded and slowed movements	10 (10.1)	2 (2.5)	0.085
Significant drowsiness, prefers to lie down all the time	18 (18.2)	2 (2.5)	0.002
Cannot stay awake	1 (1.0)	0 (0)	NA

N/A: not applicable

Table 3 - Comparison of sleep components between patient and control groups according to Pitsburg Sleep Quality Scale.

Components	Patient (score ± SD)	Control (score ±SD)	*P*-value
1 Subjective sleep quality	1.18±0.87	1.04±0.79	0.324
2 Sleep latency	1.33 ± 1.02	1.13 ±0.85	0.205
3 Sleep time	1.04±0.99	0.93±1.09	0.286
4 Sleep activity	0.57±0.93	0.35± 0.80	0.054
5 Sleep disorder	1.15±0.61	1.08±0.50	0.312
6 Drug use	0.07±0.36	0.11 ± 0.45	0.492
7 Daily functions	0.98±0.95	0.60 ± 0.84	0.004
Total score	6.32±3.62	5.23 ± 3.25	0.031
Poor sleep quality (score >5)	57 (57.6%)	38 (47.5%)	0.179

categories were presented in Table 4. In the results, the rate of OSA risk was not different in both groups (p=0.443).

STOP-BANG questionnaire: On the STOP-BANG Questionnaire, is the other test we applied to investigate the risk of OSA. We used the value of 3 as cut-off for the STOP BANG questionnaire. The mean scores were similar (1.94 ± 1.17 vs 2.20 ± 1.59; p=0.581). The comparison of proportions of high-risk patients in the both groups was found to be statistically insignificant (28.3% vs 32%; p=0.331).

Beck depression inventory. As a result of the evaluation of the depression inventory responses, by dividing the patients into mild/minimal depression and severe/moderate depression. The rate and number of severe/moderate depression in the patient group was significantly higher (41.4% vs 22.5%; p=0.007)

Table 4 - Obstructive sleep apnea risk evaluation of patient and control groups by Berlin Survey.

Category	Patient (n=99)	Control (n=80)
1 (≥2 questions)	26 (26.2%)	22 (27.5%)
2 (≥2 questions)	32 (32.3%)	17 (21.2%)
3 (≥2 questions)	12 (12,1%)	15 (18.8%)
Total: (≥2 categories)	19 (19.2%)	11 (13.8%)

Discussion. In this study, from the PSQI, we found that sleep quality was impaired in HIV-infected patients, regardless of OSA probability. In one study, Ning et al[1] found poor sleep quality in HIV-infected patients. In patient group, insomnia (23.7% vs 19.8%), decreased sleep quality (24.1% vs 19.9%) and long sleep duration (16.1% vs 8.7%) were higher.In contrast to this study, in our research, loss of daytime function was significantly higher in patients compared with controls. The result of the Stanford Sleepiness Scale, which was also used in our study, also supported the loss of daytime function.

The causes of HIV-related sleep disorders are still not clearly understood. However, it is also known that one of the common side effects of many of the ARTs used is sleep disturbance.[6] In a study in which 522 individuals living with HIV in Australia participated, sleep disturbance was reported as the most common side effect of ARTs.[17] Sleep disturbance symptoms were found to be 2,299 times higher in persons using EFV-containing regimens than in persons not using EFV.[3] We did not include patients using EFV-containing regimens in our study, because such regimens are known to have sleep disturbance adverse effects. However, more comprehensive studies should be carried out to

investigate the side effects of different ART regimens on sleep.

Obstructive sleep apnea is also among the defined factors affecting sleep quality. Metabolic disorders, such as high BMI, diabetes and hypertension, are known to have association with OSA.[2] Looking at studies examining the risk of OSA in in HIV infected people, some studies have reported that the risk of sleep apnea in individuals living with HIV is higher than in controls.[5] However, in a study conducted in Taiwan, the risk of sleep apnea was found to be lower than it was in healthy individuals.[18] In the statistical analysis of the STOP-BANG and Berlin inventories, we found that there was not difference. Our data showed similar results to the study of Chen et al.[4] Our study was designed to have similar BMI indices, in addition to the age of patients and gender profiles, for the patient and control groups. In a study by Asgari et al., it was found that increased OSA risk was associated with an especially high BMI.[5]

Our study revealed, HIV-infected patients were found to had higher depression rates than the control group. Depression and sleep disorders almost always occur together. Although it is challenging to investigate the reason-impact association between these 2 disorders, it is known that sleep disorders precede episodes of depression.[2] The scales that are used to assess depression are related to sleep patterns. High sleep disturbance prevalence has also been observed in patients in depression group.[19] A review in the United Kingdom found that depression and sleep disturbance were more common in people living with HIV than in the normal population.[20] In many studies investigating the causes of sleep disorders in HIV-infected individuals, depression has come to the forefront. In a study by Redman et al,[16] which evaluated HIV-infected individuals, it was found that people with moderate to severe depression also had poor sleep quality. In our study, we found depression rate was higher in HIV-infected individuals.

Sleeping pills, stimulants, and anti-depressants can relieve symptoms in the short term. However, we may also encounter undesirable negative results in patients with long-term use of such pharmacological substances.[6] From the perspective of our study, the measures to be taken to eliminate depression and anxiety causing sleep disorders in patients, as well as treatment plans, should be carefully examined. Moreover, the substance use history of the patients should not be ignored in the selection of treatment, and support from psychiatrists should be sought.

When many studies on sleep disorders are examined, they show a significant relationship between income level and sleep disorders. It has been observed that people with low income levels sleep worse than those with medium and high income levels.[21] Barriers to accessing ideal living conditions affect the individual's stress level, thus disrupting the circadian cycle. Therefore, socioeconomic status (SES) may contribute to sleep disorders.[22] In addition, the lifestyle, psychology and behavior of the individual are extremely important in terms of sleep health. Like low SES, behavioral risk factors, such as smoking, alcohol and drug use, or eating disorders also negatively affect sleep quality.[23] In our study, SES could not be evaluated clearly because we could not reach a sufficient number of patients. However, further examination of sleep disorders, taking into account the impact of SES, will contribute to how social inequalities can cause sleep disorders and will guide prevention and treatment.[22]

Study limitations. Although many studies in the literature investigating the causes of sleep disorders in HIV-infected individuals have emphasized such factors as sleep apnea, high BMI, the ART regimens used and depression, these results that we found, suggest that depression may be the most likely cause of sleep disorders. However, our study has the following limitations: i) The education and sociocultural status of the patients were not evaluated. ii) The HIV infection diagnosis time, which is one parameter that may affect depression and sleep quality, differed between patients. Moreover, the relationship between disease duration, treatment options and sleep was not evaluated in our study. iii) Presence of OSA was determined by a questionnaire. It would also have been more useful to use validated diagnostic tools, such as polysomnography, which is used to determine sleep characteristics, rather than using subjective scales to detect sleep disorders. iv) Our patient and control groups were not overweight and had normal BMIs.

In conclusion, the most important factor affecting sleep quality in individuals living with HIV is depression. Accordingly, we determined that individuals living with HIV should be examined in more detail in terms of sleep disorders at the time of diagnosis. Moreover, causes of sleep disorders should be determined accurately, and support should be sought from relevant experts.

Our study is different from many of the previous studies that investigated the causes of sleep disturbances in HIV infected patients, in that it was a study that included a control group. The findings of this study and other studies on individuals living with HIV highlight a need for more comprehensive studies on the reasons for impairment of the sleep quality of individuals living with HIV and the precautions to be taken to

prevent such impairment. In light of our current study, future studies on this topic should be prospective and investigate the change in sleep quality of HIV-infected individuals with depression and sleep disorders after depression treatment.

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