Differences in Circadian Sleep Parameters as a Function of Gender in Patients on the Waiting List for Liver Transplantation

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ABSTRACT

Sleep is a critical component of health, yet its role is underexplored in patients awaiting organ transplantation. This study examined sex-based differences in circadian sleep indicators among liver transplant candidates. Fifty patients (40 men (M) and 10 women (W)) on the waiting list at Hospital Clínico Universitario Virgen de la Arrixaca (Murcia, Spain) wore the Kronowise K6 wrist device on their nondominant wrist for 1 week pre-transplantation. Data were analysed using Kronowise 100 software (Kronohealth, Spain). Forty-two variables related to sleep quality and circadian rhythms were assessed via Student's t-test. Significant differences between sexes emerged in actual sleep time (p = .03), sleep efficiency (p = .022), total movement time (p = .011), and blue light exposure before sleep (p = .04). Men exhibited longer sleep duration, greater movement, and higher pre-sleep light exposure, whereas women demonstrated superior sleep efficiency. The midpoint of sleep-related peak values occurred later in women. Despite shorter sleep duration, women achieved better sleep quality, potentially due to reduced exposure to blue light before sleep, which was up to 2.5 times less than that of men. This disparity likely reflects differing pre-sleep behaviors, such as screen use. Additionally, women's core sleep phase was delayed by approximately 30 minutes. These findings suggest sex-specific differences in circadian sleep profiles among liver transplant candidates. Given men's less favorable sleep hygiene, targeted interventions may be warranted to improve pre-transplant sleep health.

PATIENTS on the waiting list for liver transplants are usually very well monitored from a medical point of view. However, it is not always the case that a holistic approach is taken to these patients by monitoring the quality of fundamental health factors such as sleep, nutrition, and physical activity levels. This holistic approach has already been proposed for certain liver diseases [1]. Biological rhythms regulate most metabolic and physiological functions in mammals. They are generally adjusted by a central clock in the central nervous system, controlled by the suprachiasmatic nucleus and linked to oscillators in each organ. These rhythms can have different durations, but they are generally circadian (Latin, circa = about, diano = day) and are synchronized with biological events (zeitgeber) such as different food intakes throughout the day or the day/night cycle.

Chronic liver disease can cause disruption of circadian rhythms of sleep, temperature, movement, etc., because of the clinical condition itself, including the presence of hepatic encephalopathy, such as alterations in blood count or biochemical parameters.

Sleep disturbances have not been well studied in patients with chronic liver disease awaiting liver transplantation. Biological rhythm disturbances have sometimes been observed, affecting men and women differently. Therefore, this study aimed to compare circadian sleep parameters in men and women on the liver transplant waiting list.

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MATERIALS AND METHODS

Patients

The patients included were those recruited for the Cronorgan21 project (Carlos III Health Institute, PI20/00981). The project was approved by the bioethics committee of the Virgen de la Arrixaca University Hospital and by the Murcia Institute for Biomedical Research (IMIB).

The results of 50 patients were analyzed; 40 men and 10 women, with a mean age of 59.3 ± 10.1 years (men = 59.8 ± 11.0; women = 57.8 ± 6.8), and body mass index (BMI) of 26.5 (M = 27.1 ± 6.3; W = 24.8 ± 3.5) and a model for end-stage liver disease (MELD): MELD score of 15.2 (M = 15.6 ± 6.3; W = 14 ± 5.6).

Patients were recruited at the time of inclusion on the waiting list, after signing an informed consent form. The inclusion criteria were (1) being over 18 years of age, (2) being on the waiting list for liver transplantation, (3) having sufficient cognitive ability to sign the informed consent form, and (4) sufficient guarantee of treatment adherence. The reasons for exclusion were (1) retransplantation, (2) patients with insufficient capacity to understand the informed consent form, (3) patients who refused to sign the informed consent form, and (4) patients who did not offer sufficient guarantees of treatment adherence.

None of the patients were working, and all were on sick leave, so they were not subject to night shifts that could cause alterations in their circadian rhythm.

Ambulatory Circadian Monitoring

Ambulatory Circadian Monitoring was carried out using the Kronowise device (Kronohealth). The device was placed on the non-dominant wrist of the patients for 7 days from the moment of inclusion in the study. The device continuously collects data on total light and blue light received, movement (acceleration and time), patient posture, and distal temperature. Once the data were collected, they were analyzed using Kronoware 10.0 software (Kronohealth SL). The device specifications have been published previously [2].

Forty-two parameters related to sleep quality (Lighs off and on (hh:mm), sleep onset and end time (hh:mm), sleep latency (min), total sleep time (min), Wake After Sleep Onset (WASO) (min), number of awakenings/h, sleep efficiency (%), actual sleep time (min), nap duration (min) and nap frequency, light received 2 hours before, during sleep and 2 hours after sleep; blue light received 2 hours before, during sleep and 2 hours after sleep, average activity 2 hours before, during and 2 hours after sleep and total time in bed) or circadian rhythm for distal temperature, movement in time and acceleration, light and sleep: Mean, Interdaily Stability (IS) (constancy of the 24 hours rhythmic pattern over days), Intradaily Variability (IV) (fragmentation of the rhythm), Relative Amplitude (RA), Normalized Amplitude (NA), Circadian Function Index (CFI) (robustness of the rhythm), as previously reported [3,4], the mean of the variable (MEAN), Circadian Health Index (CHI), Circadianity Index (CI) and Environmental Synchronization (ES), Average value of the 10 consecutive hours of maximum values (VM10), Central hour in decimal format of the 10 consecutive hours of maximum values (HM10), Average value of the 10 consecutivehours of minimum values (VL10), Central hour in decimal format of the 10 consecutive hours of minimum values (HL10), Average value of the 5 consecutivehours of maximum values (VM5), Central hour in decimal format of the 5 consecutive hours of maximum values (HM5), Value of the 5 consecutivehours of minimum values (VL5), Central hour in decimal format of the 5 consecutive hours of minimum values (HL5).

Comparisons were made using non-parametric two-way comparison tests using Mann-Whitney U.

RESULTS

Differences were found for sleep latency (M = 20.4 ± 3.2 vs W = 11.5 ± 1.7; p = .017), average activity during the 2 hours before sleep (M = 7.1 ± 0.6 vs W = 10.0 ± 1; p = .001), and average activity during the first two hours after sleep (M = 11.4 ± 0.7 vs W = 16.6 ± 1.4; p = .006), distal temperature IV (M = 0.0023 ± 0.0004 vs W = 0.0051 ± 0.0009; p = .012), nap frequency (M = 1.1 ± 0.1 vs W = 0.8 ± 0.1; p = .016), total light during sleep (M = 1.21 ± 0.5 vs W = 14.1 ± 10.7; p = .34) and blue light during sleep (M = 0.4 ± 0.2 vs W = 5.7 ± 4.2; p = .027) and in the M5 value for Tmov (M = 12.1 ± 0.7, W = 15.5 ± 1.3; p = .039). However, if we remove one woman from the analysis who is an outlier because she consistently receives a lot of light during sleep, the differences between men and women disappear for total light and blue light during sleep (M = 1.23 ± 0,5 vs W = 3.6 ± 2.12; p = .120; M = 0.4 ± 0.2 vs W = 1.1 ± 0.7, p = .144).

Regarding latency, it was observed that 34.3% of men patients had a latency greater than 20 minutes and 20% less than 8 minutes, which are the limits established as pathological. When analyzing women, 10% had a latency of less than 8 minutes and 10% had a latency of more than 20 minutes (with a value of 21 min). Although the differences were not significant, there was a numerical difference in efficiency, with 82% for men vs 86.4% for women.

The other variables analyzed did not show significantly different results between sexes.

DISCUSSION

This study found differences between men and women in both sleep-related parameters and circadian movement parameters. Differences between men and women in sleep/wake rhythms had already been observed, and differences depending on sex in the effects of rhythm disruptions have even been described [5].

The aim of this study has always been to establish differences between men and women with the intention of seeing whether there are differences that would justify differential treatment depending on sex. In this case, the first interesting difference is sleep latency. Women fall asleep earlier and have virtually no insomnia or short latency disturbances. However, men have more sleep disturbances before transplantation; almost a quarter suffer from insomnia, while another quarter have short latency, which is often associated with excessive daytime sleepiness. It should be noted that a latency period of between 10 and 20 minutes is considered normal, while a latency of less than 5 minutes is considered pathological sleepiness, and less than 8 minutes is considered sleepiness [6]. On the other hand, latency greater than 20 minutes is related to insomnia. One of the main differences observed is the frequency of insomnia, which is much higher in men than in women, with latency periods of up to 92 minutes even being recorded. Even the woman classified as an insomniac had a latency period of 21 minutes, slightly exceeding the 20 minutes considered normal. Another relevant factor is physical activity before and after sleep. Women show greater activity before sleep, which probably results in greater activity during the first two hours of sleep. We can speculate that women probably spend more time on domestic tasks before going to sleep. Another factor that could influence the outcome is the presence of hepatic encephalopathy, although when this variable is introduced into the analysis, it is found not to have an influence. Encephalopathy is more common at the time of inclusion on the waiting list in women than in men.

About light received during sleep, the amount of light received generally corresponds to the emission of a smartphone-type device. Considering that the most popular devices in Spain have a 6.1-inch screen (15 cm x 7.5 cm) [7], this amount is consistent with women who have a phone that emits 300-500 nits. What seems clear is that women are more likely to fall asleep with a device with the screen on, which could be related to the low latency they demonstrate or to their level of activity before going to sleep, which causes them to fall asleep without turning off the device.

The authors are aware that one of the weaknesses of this study is the imbalance between the number of patients on the waiting list for each gender. However, it does reflect the people who were placed on the waiting list between 2021 and 2022.

Even so, it can be concluded that women and men have differences in objectively measured sleep quality; women fall asleep more quickly after engaging in greater physical activity two hours before going to bed, with more time spent moving during the five hours with the most movement, receive more light during sleep, and have more physical activity during the first two hours after sleeping. Therefore, it seems advisable to place greater emphasis on sleep hygiene in women, such as reducing pre-sleep activity or avoiding exposure to light during sleep.

DATA AVAILABILITY

The data that has been used is confidential.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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