Article published online: 2023-04-19

Insomnia Severity is Associated with Morning Cortisol and Psychological Health

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Sleep Sci 2023;16:92–96.

Abstract

Studies suggest associations between cortisol and sleep, and cortisol shows a profound diurnal rhythm. The evidence about the relationship between chronic insomnia and cortisol is mixed. Chronic insomnia is associated with the risk of mental health disorders. The aim of this study was to evaluate the association of insomnia severity and objective sleep pattern with morning cortisol level and psychological health. The instruments used were the Insomnia Severity Index (ISI), polysomnography, Beck Depression Inventory (BDI), and Profile of Mood States (POMS). Serum cortisol was analyzed by chemiluminescence. The data revealed significant positive correlations of ISI with morning cortisol level ($r = 0.37$, $p = 0.03$), BDI score ($r = 0.44$, $p < 0.01$), and POMS-tension anxiety ($r = 0.39$, $p = 0.02$). Sleep stages N2 and N3 were correlated with POMS-fatigue ($r = 0.46$, $p < 0.01$; $r = -0.37$, $p = 0.04$). Sleep stage N3 was also negatively correlated with POMS-tension-anxiety ($r = -0.36$, $p = 0.04$). Higher insomnia severity was associated with higher morning cortisol, depression, and tension-anxiety. Sleep stage N2 was associated with higher fatigue and N3 was associated with lower tension-anxiety and fatigue.

Keywords
- sleep initiation
- sleep disorders
- sleep maintenance
- depression
- anxiety

Introduction

Insomnia is a prevalent disorder worldwide. It is characterized by difficulty initiating sleep, and/or maintaining sleep, and/or early-morning awakening with inability to return to sleep. Having significant distress or impairment in social, occupational, educational, academic, behavior or other important areas of functioning is also a component of the definition of insomnia. Moreover, sleep difficulty should occur at least 3 times/week, for at least 3 months, despite adequate opportunity for sleep, and not be explained by other sleep disorders, abuse of substance, coexistent mental disorders, or medical conditions.[1,2]

Chronic insomnia has been hypothesized to be linked with hyperarousal during sleep and wakefulness.[3] Consistent with a disorder of central nervous system hyperarousal, a 24 h increase of adrenocorticotropic hormone and cortisol secretion has been observed in individuals with chronic insomnia.[4]

Cortisol shows a profound diurnal rhythm.[5] The evidence about the relationship between chronic insomnia and cortisol level is mixed. Many studies have reported that

received
January 19, 2022
accepted
May 25, 2022

DOI https://doi.org/10.1055/s-0043-1767754.
ISSN 1984-0659.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

individuals with insomnia have elevated levels of cortisol at night,[3] and other studies indicate that low morning levels of cortisol are associated with poor sleep.[6] However, more recently, higher morning cortisol levels were found to be associated with sleep duration of less than 5 h in patients with chronic insomnia.[7]

Time of day differences in cortisol in patients with insomnia were more directly analyzed in a recent meta-analysis.[8] The increase in cortisol levels was reported to be particularly robust during the day and before bedtime. Additionally, a medium effect size was found indicating elevated morning levels of cortisol in individuals with insomnia, though there was high heterogeneity of these effects across studies.[8]

Considering the recent evidence suggesting morning cortisol level can be elevated in patients with chronic insomnia, the 24-h hyperarousal state hypothesis, and evidence that chronic insomnia is a risk factor for mental health disorders,[9] the aim of this study was to evaluate the association of insomnia severity and objective sleep with morning cortisol level, and psychological health in patients with chronic insomnia. The result of this study could add to literature regarding the association of cortisol level with chronic insomnia.

Material and Methods

Ethical approval for all experimental measures was granted by the university's Human Research Ethics Committee (Universidade Federal de Goiás, #1.998.334) and conformed principles outlined in the Declaration of Helsinki. Data for this study were collected in the baseline period for a study focused on the treatment of insomnia with exercise plus acupuncture (clinical trial registration #NCT03171519).

Participants and Screening

Participants were recruited through newspaper advertisements and online media. Prospective participants contacted the researchers and were initially screened in a phone interview. Inclusion criteria were: (a) aged $\geq$ 25 and $<$ 60 years; (b) diagnosis of chronic insomnia based on a combination of criteria from the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V)[1] and the International Classification of Sleep Disorders (ICSD-3).[2] These criteria were further operationalized as difficulties initiating and/or maintaining sleep at least 3 nights per week; insomnia duration longer than 3 months; and significant distress or impairment of daytime functioning. The exclusion criteria were: (a) use of psychoactive drugs (treatment or abuse); (b) history of psychiatric diseases (for example: major depression, generalized anxiety disorder, or panic syndrome); (c) shift working (non-regular sleep-wake cycle).

Prospective participants who passed a phone screening were invited to the sleep clinic for further orientation. During the visit, the prospective participants signed a written informed consent form approved by the ethics committee.

Design

The protocol included two visits to the sleep laboratory. In the first visit, the participants filled out questionnaires to evaluate insomnia severity and psychological health. In the second visit, the participants were submitted to a polysomnography (PSG), and a blood sample was collected on the subsequent morning.

Measures

Insomnia Severity Index (ISI)

The ISI assessed insomnia-related complaints. It is a short and easy self-applied scale with 7 items scored from 0 to 4, with a total score varying from 0 to 28. The total score is interpreted as follows: absence of insomnia (0–7); subthreshold insomnia (8–14); moderate insomnia (15–21); and severe insomnia (22–28).[10]

Polysomnography

The PSG was performed using the iCelera, *iBlue*, version 1.1.39, (iCelera Tecnologia em Equipamentos Médicos Ltda., São Paulo, SP, Brazil) device at different periods of 30-second windows classified as awake, sleep stages N1, N2, and N3 (non-rapid eye movement–NREM), and REM (rapid eye movement) sleep according to the criteria standardized. Four electroencephalogram (EEG) leads (C3-A2, C4-A1, Fz-A1, and O1-A1), 2 electrooculogram (EOG) channels (C3), 2 electromyography (EMG) channels (submental and legs), and 1 electrocardiogram (ECG) lead (modified D2) were recorded. The recording started according to patient's habitual bedtime and finished at 7 am. The sleep variables analyzed were total sleep time (TST), sleep efficiency (SE; ratio between total sleep time and total time of recording multiplied by 100), sleep onset latency (SOL), REM latency (LREM), wake time after sleep onset (WASO), arousals, apnea hypopnea index (AHI), periodic leg movements (PLM), and percentage of sleep stages. The analysis of PSG was carried out by two investigators who used international criteria and were blind to the grouping of the volunteers.

Psychological Health

Depression symptoms were assessed with the Beck Depression Inventory (BDI).[11] It is a 21-question multiple-choice self-reported inventory with answers that comprise scores range from 0 to 3 (absent, mildly, moderately, and severely). The minimum score is 0 and the maximum score is 63. The BDI criteria scores are: 0 to 9 minor or no depression symptoms; 10 to 18 mild depression symptoms; 19 to 29 moderate depression symptoms; and 30 to 63 severe depression symptoms.

The Profile of Mood States (POMS) was the instrument used to evaluate mood states. It has 65 items and 6 domains: tension-anxiety, depression, anger-hostility, vigor-activity, fatigue, and confusion/bewilderment. The total mood disturbance score is derived by subtracting the vigor/activity score from the sum of scores from the other subscales.[12]

Morning Cortisol Level

Blood sample was collected at 08:00 ± 1 h at the sleep clinic following the PSG, before the participants ate, drank, or brushed their teeth. Serum cortisol was analyzed by chemiluminescence.

Data Analysis

The TIBCO STATISTICA software, version 13.5, (TIBCO Software Inc., Palo Alto, CA, USA) was used for analysis. Considering some variables did not present normal distributions in the Shapiro-Wilk test, Spearman rank-order correlations were conducted to assess whether insomnia severity (ISI score) and objective sleep (evaluated by PSG: sleep onset latency, REM latency, wake after sleep onset, total sleep time, sleep efficiency, stages N1, N2, and N3, and REM sleep) were associated with cortisol level, depression, and mood. Data are presented as mean (standard deviation [SD]). Significance level was set at $p < 0.05$.

Results

Thirty-four patients (29 female), with mean age of 45.3 ± 8.1, were included in this study. ►**Table 1** shows the insomnia severity, PSG data, BDI, POMS, and morning cortisol data level. The mean ISI score showed that the patients had moderate insomnia, on average. The BDI data revealed mild depression symptoms, and wakefulness after sleep onset (WASO) revealed that the patients had sleep-maintenance insomnia. The PSG data of 2 patients were lost (n = 32).

Table 1 Insomnia severity, polysomnographic data, depression, mood profile, and morning cortisol level of patients with chronic insomnia.

Insomnia Severity Index (score) n = 34	17.5 ± 3.8
Polysomnography n = 32	
Sleep onset latency (min)	10.9 ± 9.9
REM latency (min)	132.3 ± 60.5
Wake after sleep onset (min)	68.2 ± 33.7
Total sleep time (min)	419.8 ± 71.1
Sleep efficiency (%)	84.2 ± 8.2
Stage N1 (%)	6.4 ± 4.8
Stage N2 (%)	53.3 ± 9.9
Stage N3 (%)	24.2 ± 9.5
REM sleep (%)	16.1 ± 5.7
Beck Depression Inventory (score) n = 34	15.9 ± 7.1
Profile of Mood States (score) n = 34	
Total mood disorder	37.7 ± 34.3
Tension/anxiety	11.3 ± 7.2
Depression	14.5 ± 11.1
Anger/hostility	13.0 ± 9.6
Vigor/activity	16.0 ± 5.2
Fatigue	11.0 ± 5.5
Confusion/bewilderment	4.1 ± 4.4
Cortisol level (mcg/dL) n = 34	14.6 ± 4.8

Abbreviation: REM, rapid eye movement.
Data are presented as mean ± SD.

Insomnia severity index correlated positively with morning cortisol level (►**Fig. 1a**), BDI score (►**Fig. 1b**), and POMS-tension/anxiety (►**Fig. 1c**). In addition, N2 sleep correlated positively with POMS-fatigue (►**Fig. 1d**), and N3 sleep correlated negatively with POMS-fatigue (►**Fig. 1e**) and POMS-tension/anxiety (►**Fig. 1f**).

Discussion

In the present study, higher insomnia severity was associated with higher morning cortisol level, depressed mood, and tension-anxiety. It is well established that 24-h cortisol secretion is significantly higher in individual with insomnia, compared with normal controls, and in the 24-h period, the greatest elevations have been observed in the evening and first half of the night.[13]

A short average sleep duration (< 6 h/night) has been associated with a less pronounced late decline in cortisol.[14] In another way, some previous studies have showed that insomnia with objective short sleep duration (< 5 h) is associated with higher cortisol level measured when awake[7] or closer to midday,[15] and, in a recent study, higher diurnal cortisol was found in patients with insomnia and higher arousal.[16] A recent meta-analysis reported a medium-sized effect linked with the association of insomnia with morning cortisol levels.[8] Despite mixed results, in the persistent insomnia disorder, cortisol appears to be upregulated. There is accumulating evidence for basal levels of cortisol to be elevated in patients with anxiety disorders.[17]

In the present study, we observed an association of insomnia severity with depression and tension-anxiety symptoms. Extensive literature has linked insomnia with mental health disorders. Depression has been identified as the most common mental health condition comorbid to insomnia. In addition, higher levels of cortisol are a risk for subsequent depression.[18]

We also observed an association of higher percentage of N2 sleep and lower percentage of N3 with a higher POMS-fatigue sub-score, and higher percentage of N3 sleep correlated with a lower tension-anxiety sub-score. Previous studies have showed insomnia patients are more likely to switch from deep to light sleep and from N2 sleep to wakefulness.[19] Fatigue is a common daytime consequence of chronic insomnia.[1] Sleep stage N3 is a regenerative period in which your body heals and repairs itself. Higher slow-wave sleep is associated with lower anxiety and fatigue.

The mechanisms could explain the relationship of N3 sleep with anxiety and fatigue in patients with chronic insomnia are uncertain, but previous studies reported the action exerted by the stress hormones is mediated by mineralocorticoid receptor, which are expressed abundantly in the limbic circuitry, particularly in the hippocampus. Limbic mineralocorticoid receptors are downregulated by

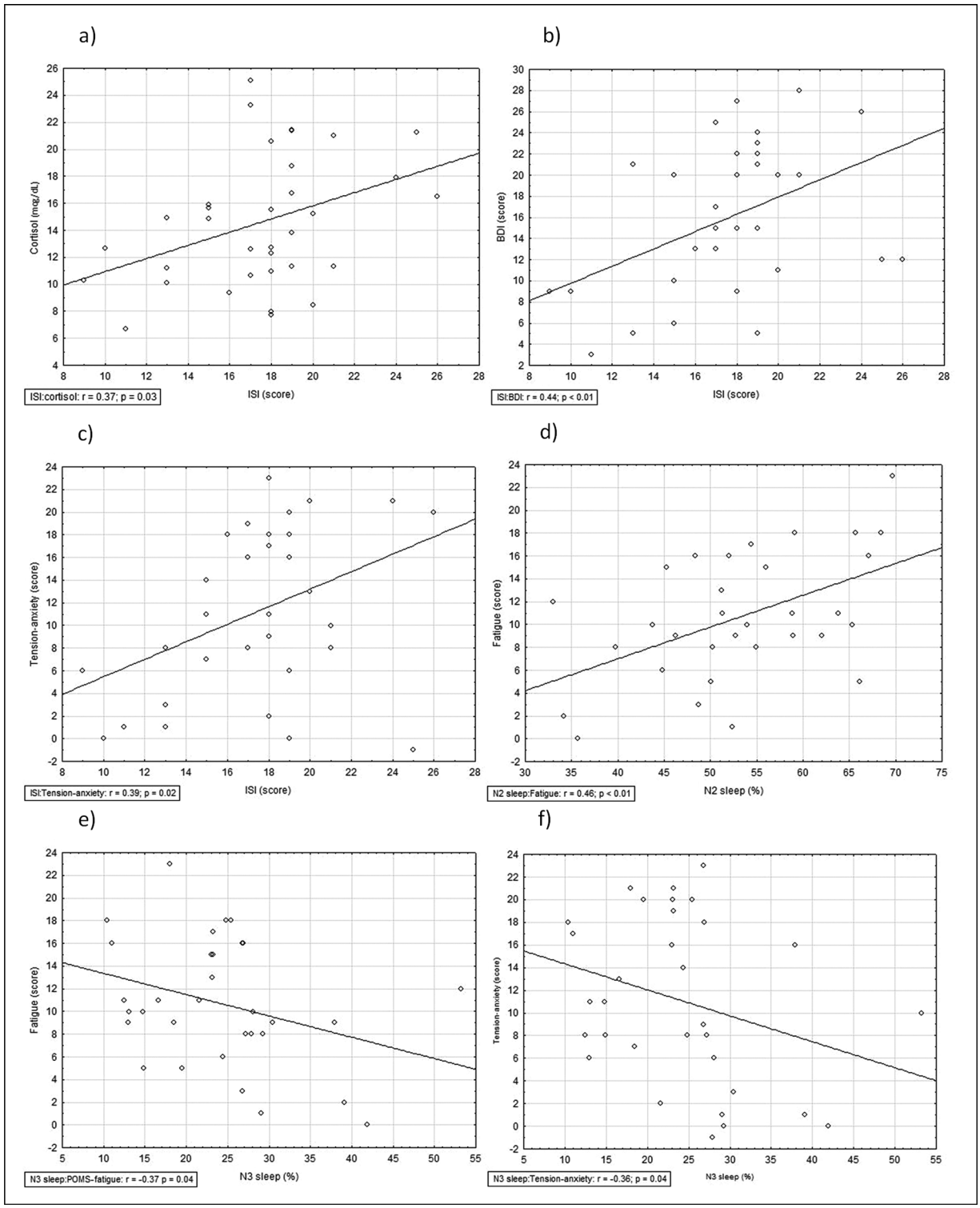

Fig. 1 Correlation of insomnia severity index (ISI) with morning cortisol level (**a**), BDI (**b**), and POMS-tension/anxiety (**c**). Correlation of N2 sleep and N3 sleep with POMS-fatigue (**d, e**). Correlation of N3 sleep with POMS-tension/anxiety (**f**).

chronic stress and during depression. Increased mineralocorticoid activity inhibits hypothalamic-pituitary-adrenal axis activity, promotes slow wave sleep, and reduces anxiety.[20]

This study has several strengths. These included PSG sleep, patients clinically diagnosed with chronic insomnia, and measures of the blood cortisol.

This study also had limitations. First, correlations do not establish causality. Second, there was an absence of more specific exclusion criteria concerning clinical disease and/or drugs that could affect sleep. Third, the sample size was small.

In conclusion, the higher cortisol observed after awakening in patients with higher severity of insomnia corroborates

previous evidence showing that patients with chronic insomnia have a state of 24-h hyperarousal. In this sense, as suggested previously, the experience of chronic insomnia might not be explained by patients' misperceptions, but instead might be the result of a dissociation between arousal and sleep-inducing brain systems. Consistent with previous studies, insomnia was associated with depressed mood and anxiety, lighter sleep was correlated with higher fatigue, and deep sleep was correlated with lower anxiety. In clinical practice, identifying the hyperarousal state in patients could direct the prognosis and treatment of this sleep disturbance.

Conflict of Interests
The authors have no conflict of interest to declare.

Acknowledgements
The authors would like to thank all participants who volunteered their time to take part in this study and the institutions that made this study possible, CNPq, NEUROCOR/Jataí, GO, Plena/Jataí, GO, Hospital Padre Tiago/Jataí, GO.

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