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ORIGINAL PAPER

Altered sleep architecture and higher incidence of subsyndromal depression in low endogenous melatonin secretors

Shadab Ataur Rahman · Shai Marcu · Leonid Kayumov · Colin Michael Shapiro

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Abstract Melatonin secretion is synchronized to the sleep/wake cycle and has been suggested to have somnogenic properties. Sleep/wake cycle disruption and alterations in the secretary pattern of melatonin is present in various psychiatric disorders. The objective of this study was to investigate the sleep architecture and the presence of depression in individuals with low endogenous melatonin levels. The study included 16 participants (mean age 30.3 ± 14.9 years). The first night of testing included psychiatric evaluation followed by melatonin secretion profile evaluation by Dim Light Melatonin Onset test and then standard montage polysomnographic testing. On the second night, only polysomnographic testing was carried out with an imposed sleep period of 8 h. Low endogenous melatonin secretors (LEMS) showed no discernible peaks in melatonin secretion compared to normal secretors (controls). LEMS demonstrated significant alterations in rapid eye movement sleep but not in non-rapid eye movement sleep along with poor sleep initiation and quality compared to controls. 55.6% of the low melatonin secretors group presented with subsyndromal depression. Melatonin has significant bearing on sleep architecture and a lack of melatonin may desynchronize endogenous rhythms allowing subsyndromal depression to manifest.

Keywords Circadian rhythm disorder · Subsyndromal depression · Low melatonin · Sleep architecture

S. A. Rahman · C. M. Shapiro
Sleep Research Laboratory, University Health Network, Toronto, ON, Canada
e-mail: rahman@mshri.on.ca

S. Marcu · L. Kayumov · C. M. Shapiro
Department of Psychiatry, University of Toronto, Toronto, ON, Canada

S. Marcu · C. M. Shapiro
Youthdale Child and Adolescent Sleep Centre, Toronto, ON, Canada

C. M. Shapiro
Department of Ophthalmology, University of Toronto, Toronto, ON, Canada

C. M. Shapiro (✉)
Toronto Western Hospital, MP7 # 421, 399 Bathurst St., Toronto, ON M5T 2S8, Canada
e-mail: suzanne.alves@uhn.on.ca

Introduction

Melatonin (5-methoxy *N*-acetyltryptamine) is a neurohormone secreted primarily by the pineal gland under the control of the master circadian clock, the suprachiasmatic nucleus (SCN) [6]. In humans, melatonin secretion is closely synchronized with the habitual hours of sleep, increasing soon after the onset of darkness, peaking in the middle of the night (between 0200 and 0400 hours), and then gradually returning to baseline levels by the end of the night [5, 63]. One of the principal functions of melatonin is to relay temporal queues to various organs, including the SCN itself [5, 66].

Several studies suggest a role for melatonin influencing the timing of sleep onset and sleep duration [6, 14, 34]. In humans, melatonin administration during the subjective daytime promotes sleep by inducing earlier sleep onset and generating longer sleep duration [18, 45, 58, 83]. Daily melatonin ingestion can entrain free running circadian rhythms in blind individuals [39, 40, 57] and pharmacological suppression of nocturnal melatonin secretion

increases total wake time and concomitantly decreases both non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep [73]. The circadian rhythm of plasma melatonin also has a temporal association with circadian rhythms observed in cortical EEG activity during sleep in humans [17], suggesting a direct influence of melatonin on sleep–wake regulation.

However, the effectiveness of melatonin in improving sleep depends on the nature of the sleep disorder and the timing of melatonin administration. In the elderly population, who show a decrease in melatonin secretion and often exhibit marked sleep–wake cycle alterations, only certain melatonin replacement protocols tend to improve sleep [21–23, 85]. Based on whether the sleep disorder is primary or secondary in nature, exogenous melatonin may or may not be beneficial [10, 11]. This suggests that melatonin is not directly somnogenic but instead it plays an intricate role in the timing and synchronization of the sleep–wake cycle.

Melatonin can regulate the timing of various physiologic processes other than the sleep–wake cycle [6, 12, 70]. Interestingly, melatonin concentrations are altered in patients with major depression, additionally many other circadian rhythms measured in depressive patients are abnormal [26, 50, 65]. Endogenously depressed patients have also been recognized to have clear circadian rhythm abnormalities, consisting mainly in amplitude reduction [64]. Sleep–wake cycle disorders are often associated with depression, suggesting a role for circadian rhythm misalignment in generating psychosomatic and mood disorders [26, 36, 80, 81]. Since melatonin can regulate the timing of circadian rhythms, it is likely that alterations in melatonin secretion can lead to mood disorders or depression.

Our working hypothesis for this study was that endogenous melatonin functions as synchronizer of circadian rhythms and a reduction in circulating levels of melatonin will lead to desynchronization of circadian processes leading to endogenous depression. The primary objective of this study was to examine if endogenous melatonin levels modulate sleep architecture and to investigate the possible presence of psychiatric comorbidity among this unique population of low endogenous melatonin secretors (LEMS) compared to normal melatonin secretors (control).

Methods

Sample population

A total of 16 individuals (6 females), mean age of 30.3 ± 14.9 years, participated in the study at a single sleep clinic. The group of low melatonin secretors ($n = 9$) were selected from individuals who had previously been examined for sleep disorders at the same sleep clinic and had demonstrated low endogenous melatonin secretion tested by a Dim Light Melatonin Onset (DLMO) test. The original cohort consisted of 27 individuals who were referred for circadian rhythm disorders. Within that cohort, individuals were diagnosed with sleep apnea, periodic limb movement syndrome and alexithymia. Moreover, several individuals were on regular medication including antidepressants that can alter the secretion of melatonin. Therefore, only individuals who were not on any medication and did not have any other sleep disorders were randomly called upon for participation in the study out of which nine individuals were available for the study. The control group ($n = 7$) consisted of healthy individuals recruited from a cohort of individuals who had previously been referred to the clinic for the assessment of circadian rhythm disorders based on subjective complaints of an inability to initiate sleep. The individuals who were selected for this study were diagnosed with no sleep disorders and assessed to have poor sleep hygiene which was addressed through subsequent follow-up visits to the clinic prior to this study. None of the individuals were on any regular medication including antidepressants that can alter the secretion of melatonin. All participants maintained sleep diaries for 2 weeks prior to starting the study. The mean bedtime and rising time according to the sleep logs were 0153 hours (range 0010–0313 hours) and 0748 hours (range 0622–1124 hours) for the low melatonin secretors, respectively. The mean bedtime and rising time according to the sleep logs were 2317 hours (range 2213–0122 hours) and 0823 hours (range 0513–1017 hours) for the controls, respectively. Before further testing, all major psychopathologies including schizophrenia were ruled out for both groups by conducting a mini evaluation based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [4]. All differential diagnoses resulting from sleep restriction or secondary sleep disorders were also excluded using The International Classification of Sleep Disorders [16]. All assessments were conducted by a psychiatrist trained and experienced in sleep medicine. The study protocol was approved by the Research Human Ethics Committee of the University Health Network and all patients signed consent forms prior to being assessed.

Study design

During their initial visit with the psychiatrist/sleep specialists, the participants were asked to complete a battery of questionnaires which included measures of subjective levels of sleepiness, self-esteem, depression and anxiety. All clinical interviews and questionnaires were completed during the day of this initial visit. After their initial assessment, the patients underwent a two night sleep study

comprised of self-report questionnaires, saliva sample collection for melatonin assay and a PSG which included electroencephalography, electrooculography, electromyography and respiratory monitoring. The first night involved completion of pre-sleep questionnaires, followed by saliva sample collection and PSG. Saliva samples were acquired hourly from 1900 until 0300 hours. The patients then retired to sleep and their next morning waking time was left to them to choose. An hour after waking up, they completed a series of post-sleep questionnaires. The second night sleep study involved completion of the same pre-sleep questionnaires as the previous night and all patients retired to bed at a fixed time of 2300 hours and were awoken the next morning at a fixed time of 0700 hours, thus creating an imposed sleep period. They again completed the same series of post-sleep questionnaires. No saliva samples were collected on the second night.

Sleep physiology parameters

Objective measures: two night polysomnography

A standard montage including electroencephalography, electrooculography, electromyography and respiratory monitoring (oxygen saturation, nasal airflow, and breathing effort) was used. The polysomnographs were scored by a single-blinded scorer according to standardized criteria [56]. The sleep parameters included sleep onset latency (SOL), sleep efficiency (SE%), REM latency, slow wave sleep (SWS%), REM% and arousal index (AI). SOL was defined as the first 30-s epoch of stage 2 sleep. Arousals were defined as an abrupt shift in EEG frequency, which may include theta, alpha and/or frequencies greater than 16 Hz but not spindles. Ten seconds of continuous sleep must precede the arousal. The arousal must last $\geq$3 s and it must be accompanied by an increase in chin EMG if it occurs during REM sleep [1, 8].

Subjective measures

Patients completed questionnaires pre- and post-sleep study on both nights of testing. The questionnaires were used as a subjective measure of fatigue, sleepiness, alexithymia (emotional connectedness) and alertness. The questionnaires were the Fatigue Severity Scale (FSS) [35], Stanford Sleepiness Scale (SSS) [25], Toronto Alexithymia Scale (TAS-20) [68], ZOGIM-A (questionnaire name is not abbreviated) [60], and the Toronto Hospital Alertness Scale (THAT) [60]. The THAT is a rating scale of alertness that assesses a range of activities such as ability to concentrate, think of new ideas, or focusing on the task at hand. The ZOGIM-A describes a range of activities that might impact on alertness (sleep loss, exercise, caffeine, etc.) and inquires about how a person may function differently if he or she was more alert [60].

The post-sleep study questionnaires completed in the morning after the sleep study were the FSS, SSS, ZOGIM-A, and the THAT. All questionnaires were completed an hour before retiring to bed and within an hour after waking up. In addition, subjective sleepiness was evaluated using the Epworth Sleepiness Scale (ESS) [27, 28].

Circadian rhythm parameters

Sample collection for melatonin was carried out as previously described [32, 33]. Briefly, individuals were seated in a dark room from 1900 to 0300 hours and saliva specimens were collected using the Sali-Saver^{TM} (ALPCO, American Laboratory Products Company, New Hampshire, USA). Samples from each hour were refrigerated until all samples were collected at the end of the night. Sample collection was carried out under dim red lighting (<5 lux). Saliva specimens were analyzed immediately after collection of the last sample. Salivary melatonin was determined by Direct Saliva Melatonin ELISA kit from Buhlman Laboratories (Allschwil, Switzerland). Saliva specimens from a given subject were run with the same assay kit; all kits used in this study were from the same batch. Assay functional sensitivity was 1.3 pg/ml, the maximum intra-assay and inter-assay coefficients of variability were 6.5% ($n = 12$) and 11.3% ($n = 12$), respectively (in the range of concentrations of melatonin between 1 and 81 pg/ml).

The DLMO, defined as the point at which the melatonin secretion begins, was used as a marker of the circadian phase. DLMO was defined as the time of the sampling of the first salivary sample to show an elevated melatonin measurement that remained elevated in the subsequent sampling time. To be considered elevated the melatonin concentration had to be 20% greater than the 1900 hours baseline value and greater than a minimum value of 4 pg/ml [43, 49].

Psychiatric parameters

The parameters evaluated were depression, anxiety, self-esteem and subjective perception of sleepiness. The scales used were previously validated questionnaires, namely, the Centre for Epidemiological Studies Depression Scale (CES-D) [53], the Rosenberg Scale (RS) [20], the Zung Anxiety Scale (ZAS) [86] for each of the measures, respectively. Coupled with the self-report questionnaires, the final diagnosis of subsyndromal depression was made by psychiatrists who were blinded to melatonin secretion type using the definition provided by Judd et al., "greater than, or equal to, two symptoms of depression of the same quality as in MD, but which symptoms excluded depressed mood and anhedonia. The symptoms must be present for

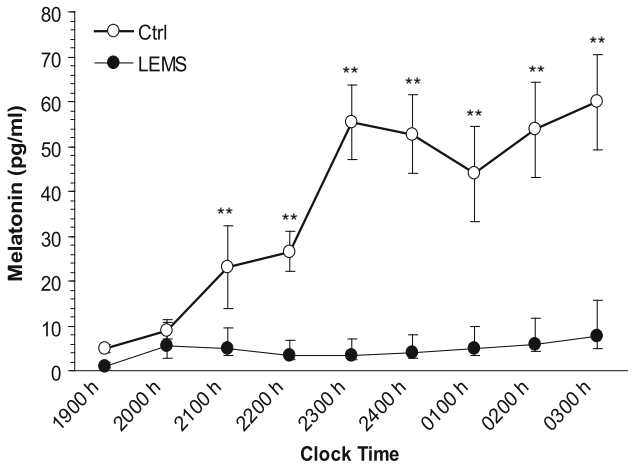

Fig. 1 Melatonin secretion profile of low endogenous melatonin secretors (LEMS) and normal secretors (controls). Saliva samples were collected hourly from 1900 to 0300 hours and batch processed by ELISA. Data shown are mean ± SEM. Circadian parameters were compared between the two groups with Student's *t* test with Bonferroni correction for repeated *t* tests for multiple variables (significance at $^{**}P < 0.001$ between LEMS and controls)

more than 2 weeks and be associated with social dysfunction" [29, 59].

Data analysis

Results are expressed as mean ± SEM. All questionnaire data were analyzed with the non-parametric Mann–Whitney test with a Bonferroni's alpha adjustment of 0.0125 for each psychiatric questionnaire and 0.01 for each sleep questionnaire. Objective sleep variables and circadian parameters were compared between the two groups with Student's *t* test with Bonferroni correction for repeated *t* tests for multiple variables. Statistical significance was set at $P = 0.05$. First and second night data were analyzed separately to negate a possible first night effect [39].

Results

Low endogenous melatonin secretors were defined as subjects with no discernible DLMO point throughout the duration of testing. Based on the melatonin secretion profile, subjects were dichotomized into groups: normal melatonin secretors (controls) ($n = 7$; 3 females) and low endogenous secretors ($n = 9$; 2 females). The mean age of the controls was 31.7 years (range 19–56 years) and the mean age of the LEMS was 27 years (range 18–53 years).

The mean amount of melatonin secreted at DLMO by the control group was 23.1 ± 9.2 pg/ml with a night time peak of 59.9 ± 10.7 pg/ml. In contrast, the low secretors had no clearly discernible peak or inflection in the rise of melatonin with the highest concentrations reaching only 7.8 ± 2.8 pg/ml. Melatonin levels were significantly higher in controls than in LEMS starting from 2100 hours (DLMO time) until the end of the testing period (0300 hours) (Fig. 1).

None of the sleep architecture parameters on the first night of testing were significantly different between LEMS and normal secretors (controls) (Table 1). While normal secretors retired to bed at 0331 ± 0112 hours, LEMS retired at 0339 ± 0021 hours. The mean wake up time for LEMS was 0908 ± 0227 hours and for normal secretors was 1054 ± 0124 hours. The second night of sleep studies with imposed sleep period revealed significant differences in four parameters between LEMS and controls (Table 1). SOL was significantly higher in LEMS (35.2 ± 7.4 min) than in controls (12.5 ± 4.2 min); SE was significantly lower in LEMS (68.9 ± 2.8%) than in controls (89.3 ± 2.1%); REM latency was significantly higher in LEMS (193.0 ± 40.5 min) than in controls (76.4 ± 7.2 min) and REM% was significantly less in LEMS (13.1 ± 3.3%) than in controls (23.6 ± 2.7%). No significant differences were noted in the pre- and post-PSG questionnaires between the groups on either the first or the second night (data not

Table 1 Sleep physiology parameters of low endogenous melatonin secretors (LEMS; $n = 9$) and the normal secretors (controls; $n = 7$)

Sleep parameter	First night		Second night	
	LEMS	Controls	LEMS	Controls
Sleep onset latency	10.9 ± 3.9	10.8 ± 3.3	35.2 ± 7.4**	12.5 ± 4.2
Sleep efficiency (%)	84.2 ± 3.5	86.1 ± 2.6	68.9 ± 2.8**	89.3 ± 2.1
Slow wave sleep (%)	18.3 ± 4.8	17.7 ± 3.7	19.7 ± 2.8	25.7 ± 8.2
REM latency	88.1 ± 16.7	58.8 ± 11.9	193 ± 3.3**	76.4 ± 7.2
REM (%)	17.8 ± 2.2	20.3 ± 4.3	13.1 ± 3.3**	23.6 ± 2.7
Arousal index	8.3 ± 2.5	8.7 ± 1.5	6.9 ± 1.3	8.4 ± 2.1

Subjects underwent full montage polysomnography for two nights. The second night of testing had an imposed sleep period from 2300 to 0700 hours. Data shown are mean ± SEM

Objective sleep variables were compared between the two groups with Student's *t* test with Bonferroni correction for repeated *t* tests for multiple variables (significance at $^{**}P < 0.001$ between LEMS and controls)

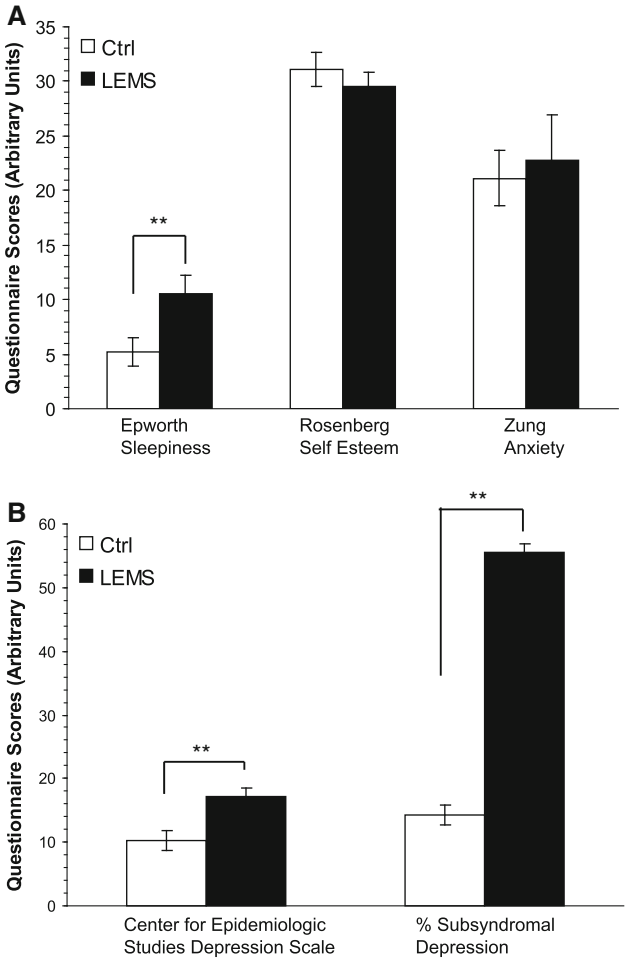

Fig. 2 Psychiatric profile of low endogenous melatonin secretors (LEMS) and normal secretors (controls). LEMS demonstrated significantly increased daytime sleepiness compared to controls with no significant differences in self-esteem and anxiety levels (**a**). LEMS demonstrated elevated depression levels and higher incidence of subsyndromal depression (**b**). Data shown are mean ± SEM. All questionnaire data were analyzed with the nonparametric Mann–Whitney test with a Bonferroni's alpha adjustment (significance at $^{**}P < 0.001$ between LEMS and controls)

shown). ESS scores were significantly higher in LEMS (10.6 ± 1.5) than in the controls (5.2 ± 1.2) (Fig. 2a).

While LEMS and controls scored comparably on the RS and ZAS, LEMS scored significantly higher on the CES-D (17.8 ± 3.0) than controls (7.4 ± 1.4) (Fig. 2a). The clinical evaluation revealed a higher prevalence of subsyndromal depression in LEMS than in controls, only 14.3% controls ($n = 1$) were diagnosed with subsyndromal depression whereas 55.6% of LEMS ($n = 5$) were diagnosed with subsyndromal depression by psychiatrists (Fig. 2b).

Discussion

Our study is the first to demonstrate that a natural reduction in endogenous melatonin secretion is associated with altered sleep architecture and sleep phase duration. A salient feature of our study design was to be able to compare the natural sleep pattern with that of an imposed sleep period which can be helpful in diagnosing circadian rhythm sleep disorders (CRSDs), sleep onset insomnia and sleep/wake cycle phase alterations [31]. While SOL levels were comparable in the controls between the first and second night of PSG testing, the LEMS had higher SOL between the first and second night suggesting that low levels of melatonin may promote sleep onset insomnia and alterations in sleep/wake cycle. Furthermore, lower SE in LEMS compared to controls demonstrates that a reduction in endogenous melatonin levels leads to poor sleep quality. A routine example of poor sleep maintenance and increased sleep fragmentation is observed in daytime sleep in shift workers who also have lower melatonin levels during the main sleep episode [2, 3, 37]. Our study also demonstrates elevated ESS levels in LEMS suggesting increased daytime sleepiness in LEMS that may be directly induced by poor sleep quality.

Individuals from both groups were awake till 0300 hours the first night due to DLMO testing and this may have caused a phase delay influencing sleep homeostatic aspects the second night. However, we did not find any significant increase in the SOL of the controls between the first and second night (with imposed sleep) of testing which would be indicative of a phase delay in the major sleep episode. Furthermore, there was no significant difference between the first and second night SWS% in controls suggesting that the participants had adequate sleep the first night and were not sleep deprived. It is possible that the control group can entrain their circadian rhythms faster than low melatonin secretors. Exposure to light after awakening entrained the normal secretors but not the low secretors. However, the differential ability in entrainment of circadian rhythms between low melatonin secretors and normal secretors requires further investigation.

We also observed significant alterations in REM latency and the amount of REM sleep (REM%) in LEMS compared to normal melatonin secretors without affecting SWS. According to the two-process model of sleep, SOL is modulated by the circadian propensity for sleep (Process C) and REM sleep has also a circadian component whereas SWS is driven by the homeostatic propensity for sleep (Process S) [9]. This suggests that melatonin is required for the finer alignment of the sleep–wake cycle especially those parameters that have a circadian component. A significant delay in sleep onset and REM sleep onset strongly suggests a shift in the circadian timing of the major sleep episode in low melatonin secretors.

Alterations in REM sleep is also associated with depression; however, these alterations are commonly seen as an increase in REM sleep and decrease in REM latency

[7, 79]. This difference in REM sleep between the individuals with subsyndromal depression as in our study and major depression as in other studies suggests that the sleep architecture alterations observed with major depression has different underlying neurobiological mechanisms than those inducing sleep architecture alterations in subsyndromal depression. It is possible that low melatonin secretors also have disrupted serotonin (5-HT) secretion [19, 46, 54]. We hypothesize that the low melatonin secretors in our study may have high higher than normal central 5-HT availability. Moreover, it may be that 5-HT levels do not differ during the day between the low melatonin producers and healthy individuals. However, nocturnal 5-HT levels are higher in low melatonin secretors than in healthy individuals due to the reduced serotonin to melatonin conversion in the low melatonin producers [67]. This excess in pineal 5-HT may then play an additive role in total central 5-HT availability and adversely affect 5-HT signaling. REM sleep expression is promoted in part by cholinergic neurons [47, 62] and inhibited by serotonergic and noradrenergic neurons in the dorsal pontine tegmentum [41]. Fluoxetine a selective serotonin reuptake inhibitor decreases REM sleep and increases REM latency in both healthy and depressed subjects [71] suggesting that increased serotonergic signaling may induce the changes in REM sleep observed in our study.

The increased SOL and REM latency suggest that there may be a delay in the sleep cycle compared to other endogenous rhythms. According to the phase advance theory of affective disorders [9, 76], the oscillator regulating endogenous rhythms has a phase that is advanced compared to the oscillator regulating sleep. This causes the patient to sleep at a time when the other rhythms are at an inappropriate phase for sleep initiation or maintenance, promoting desynchronization and depression. However, further investigation is required to determine the phase angle difference between endogenous rhythms such as body temperature and cortisol secretion and the sleep cycle in LEMS to confirm the phase advance hypothesis of affective disorders in our patient population. Prior studies have demonstrated that exogenous melatonin administration even in healthy individuals increases the amount of REM sleep obtained [13, 82], suggesting that a lack of melatonin can cause a reduction in REM sleep as observed in our study. In addition, the reduction in melatonin secretion may induce circadian desynchrony promoting the development of subsyndromal depression.

Furthermore, a steady internal and external phase relationships appear to be crucial for a stable and euthymic mood state (i.e. the timing between core body rhythms such as cortisol and temperature as well as the timing of sleep with respect to the day–night cycle) [24, 65, 80]. Any misalignment may bring with it the propensity for mood fluctuation, particularly in vulnerable individuals such as low melatonin secretors who have marked alterations in their sleep–wake rhythm. It has been postulated that alterations in circadian phase markers such as low melatonin secretion can be a biological marker for susceptibility to endogenous depression [74, 77]. Both the amplitude and rhythm of melatonin secretion can be altered in patients suffering from unipolar depression as well as in patients suffering from bipolar affective disorders [72]. Abnormal levels and patterns of melatonin secretion have been observed in depressed patients in some [15, 30, 78], but not all studies [69]. The circadian rhythm of individual components such as cortisol and melatonin rhythm, core body temperature rhythm, may have different controls and alteration in any one control is likely to have significant impacts on other circadian controls as well. Therefore, inconsistent findings may also arise from the multifactorial nature of circadian mechanisms and heterogeneity of symptoms in mood disorders. For example, a reduction in amplitude of 24-h cortisol levels is apparent in non-psychotic depressed patients, but not in patients with the psychotic subtype of depression [52]. In addition, a growing number of studies indicate that genetic vulnerability moderates the nature of circadian disturbances in mood disorders [38, 51].

Delayed sleep phase syndrome (DSPS) is a CRSD, caused by a desynchronized central biological clock [75]. DSPS patients show emotional features such as low self-esteem, nervousness and diminished control of emotional expression [61]. Our results suggest that similar to DSPS, low endogenous melatonin levels may promote alterations in the timing of the major sleep episode. However, the low melatonin secretors in our study cannot be categorized as DSPS patients based on the lack of characteristic delayed retiring times when comparing retiring times between weekdays (imposed sleeping period) and weekends (free to choose sleeping period) [44, 84], furthermore, due to the lack of a clearly discernable DLMO which is observed in DSPS patients [55].

In this present study, we used self-reporting questionnaires and psychiatric interviews to evaluate depression, anxiety and self-esteem. The presence of subsyndromal depression and high RS and CES-D scores suggests a similar pattern of depression and low self-esteem arising from underlying desynchronization of the circadian system due to a lack of melatonin and its chronobiotic properties.

Our study is the first to show that there is a very high prevalence of subsyndromal depression in LEMS. The prevalence of subsyndromal depression in the general population is 8.4% and females more frequently present with subsyndromal depression [59]. In our clinical study, 14.3% of normal melatonin secretors ($n = 1$) were diagnosed with subsyndromal depression whereas in low

melatonin secretors 55.6% ($n = 5$) were diagnosed with subsyndromal depression. Even though the number of participants in each group were low, making it a limiting factor in the present study, the high prevalence of subsyndromal depression in low melatonin secretors is alarming because of a high possibility of this condition leading to major depression. Individuals with minor or subsyndromal depression have a 5.5-fold higher risk for major depression after 1 year compared to individuals who are not depressed [42].

In addition, the age at which this population starts to exhibit such symptoms is also concerning. The mean age of low melatonin secretors was early 30s, much earlier than the observed decline in endogenous melatonin levels in elderly individuals. Similar problems of sleep/wake cycle desynchronization and subsyndromal depression with very fast progression into major depression are evident in the elderly population [42]. Though we did not look into specific causes for this early onset of melatonin decline, a hyperactive hypothalamic–pituitary–adrenal (HPA) axis may play a role since elevated cortisol levels can reduce melatonin secretion [48]. Another possibility is genetic polymorphisms and loss of function mutations in the genes coding the necessary enzymes that catalyze the reactions in the melatonin biosynthetic pathway.

To our knowledge, our study is the first to examine sleep physiology in endogenously low melatonin secretors and it demonstrates markedly altered sleep architecture in low melatonin secretors with significant sleep–wake cycle disruption. Moreover, an alarmingly high prevalence of subsyndromal depression was identified in low melatonin secretors. While previous studies have documented a correlation between circadian rhythm disruption and depression, our findings suggest a potential direct role of melatonin with depression which warrants further investigation.

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