Original Investigation

Melatonin Supplementation for Children With Atopic Dermatitis and Sleep Disturbance
A Randomized Clinical Trial

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IMPORTANCE Sleep disturbance is common in children with atopic dermatitis (AD), but effective clinical management for this problem is lacking. Reduced levels of nocturnal melatonin were found to be associated with sleep disturbance and increased disease severity in children with AD. Melatonin also has sleep-inducing and anti-inflammatory properties and therefore might be useful for the management of AD.

OBJECTIVE To evaluate the effectiveness of melatonin supplementation for improving the sleep disturbance and severity of disease in children with AD.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial used a double-blind, placebo-controlled crossover design to study 73 children and adolescents aged 1 to 18 years with physician-diagnosed AD involving at least 5% of the total body surface area. The study was conducted at the pediatric department of a large tertiary care hospital in Taiwan from August 1, 2012, through January 31, 2013. Forty-eight children were randomized 1:1 to melatonin or placebo treatment, and 38 of these (79%) completed the cross-over period of the trial. Final follow-up occurred on April 13, 2013, and data were analyzed from January 27 to April 25, 2014. Analyses were based on intention to treat.

INTERVENTIONS Melatonin, 3 mg/d, or placebo for 4 weeks followed by a 2-week washout period and then crossover to the alternate treatment for 4 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was AD severity evaluated using the Scoring Atopic Dermatitis (SCORAD) index, with scores ranging from 0 to 103 and greater scores indicating worse symptoms. Secondary outcomes included sleep variables measured by actigraphy, subjective change in sleep and dermatitis, sleep variables measured by polysomnography, nocturnal urinary levels of 6-sulfatoxymelatonin, and serum IgE levels.

RESULTS After melatonin treatment among the 48 children included in the study, the SCORAD index decreased by 9.1 compared with after placebo (95% CI, −13.7 to −4.6; $P < .001$), from a mean (SD) of 49.1 (24.3) to 40.2 (20.9). Moreover, the sleep-onset latency shortened by 21.4 minutes after melatonin treatment compared with after placebo (95% CI, −38.6 to −4.2; $P = .02$). The improvement in the SCORAD index did not correlate significantly with the change in sleep-onset latency ($r = −0.04$; $P = .85$). No patient withdrew owing to adverse events, and no adverse event was reported throughout the study.

CONCLUSIONS AND RELEVANCE Melatonin supplementation is a safe and effective way to improve the sleep-onset latency and disease severity in children with AD.

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Atopic dermatitis (AD) is a common chronic, relapsing, pruritic inflammatory skin disease affecting 15% to 30% of all children and 2% to 10% of all adults.[1] Disturbed sleep is reported in 47% to 60% of children with AD and is a major factor leading to an impaired quality of life.[2-4] At present, limited studies are available to guide effective clinical management of sleep disturbances in AD. Some investigators[5,6] have studied whether treatment targeted at skin inflammation in patients with AD also improves their sleep, but the results have been inconsistent, and most of these studies used a subjective visual analog scale rather than objective measures to evaluate sleep.

Previous studies[7] have found that reduced nocturnal melatonin secretion was associated with sleep disturbance and greater severity of disease in children with AD. Melatonin is a hormone secreted by the pineal gland and is important in sleep regulation.[8] Oral melatonin has a sedative effect and has been used for the management of insomnia and jet lag. Previous studies[9-11] have shown that melatonin could shorten sleep-onset latency and increase total sleep time and sleep efficiency, possibly owing to its ability to decrease the core body temperature.[12] Melatonin also has immunomodulatory, anti-inflammatory, and antioxidative effects,[13-15] which might improve the skin inflammation and help to maintain a functional epidermal barrier in patients with AD.[15] Furthermore, melatonin has been found to be safe with minimal adverse effects, which makes it a favorable choice for children.[9,16] Therefore, we aimed to investigate whether melatonin supplementation is effective for improving the skin inflammation and sleep disturbances in children with AD.

At a Glance

- Sleep disturbance is common in children with atopic dermatitis (AD), but effective clinical management for this problem is lacking. A reduced level of nocturnal melatonin was found to be associated with sleep disturbance and greater severity of disease in children with AD. Our study evaluated the effectiveness of melatonin supplementation for children with AD.
- After melatonin treatment, the sleep-onset latency shortened by 21.4 minutes compared with placebo (95% CI, −38.6 to −4.2; $P = .02$).
- Severity of AD also improved after melatonin treatment, with a decrease in the Scoring Atopic Dermatitis index of 9.1 compared with placebo (95% CI, −13.7 to −4.6; $P < .001$).
- No adverse events were reported throughout the study.

Methods

Study Design

We performed a randomized clinical study with a double-blind, placebo-controlled crossover design at a single tertiary care hospital in Taiwan. The institutional review committee of National Taiwan University Hospital approved the study protocol (the protocol is available in Supplement 1). This study conformed to the principles of the Declaration of Helsinki.[17] Patients or their guardians provided written informed consent.

Participants

Patients aged 1 to 18 years with physician-diagnosed AD involving at least 5% of the total body surface area were recruited from the pediatric and dermatology outpatient departments of the National Taiwan University Hospital from August 1, 2012, through January 31, 2013. Follow-up was completed on April 13, 2013. Those patients with sleep problems occurring more than 3 days per week during the previous 3 months were eligible. A *sleep problem* was defined as any difficulty with sleep initiation or maintenance that led to impaired quality of life or interfered with daytime activities for the child or for family members. Exclusion criteria included documented sleep disorders, such as dyssomnias, parasomnias, and circadian rhythm sleep disorders; neuropsychiatric disorders or any other medical condition that might produce sleep problems; or use of medication for insomnia or of antidepressants within 4 weeks before the baseline visit.

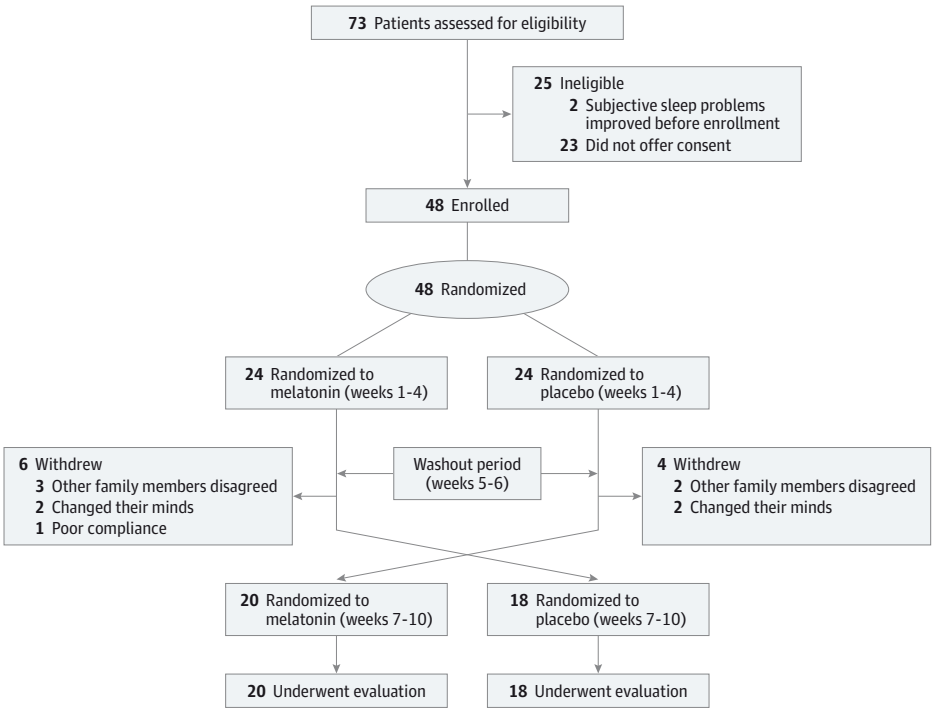
Randomization and Masking

The study participants were randomly assigned to 2 groups in a 1:1 ratio (**Figure 1**), with a block size of 4. One group received melatonin first and then placebo, and the other group received placebo first and then melatonin. Randomization was performed with a computer-generated sequence by specialized personnel who had no further involvement in the rest of the trial. The melatonin and placebo tablets were identical in appearance. The participants and their caregivers, treating physicians, those assessing outcomes, and those analyzing the data were all masked to group assignment. Allocation codes were disclosed only after the entire clinical trial was completed.

Procedures

The participants first underwent a 2-week prescreening period in which they kept a sleep diary, adhered to a fixed sleep schedule, and avoided caffeinated drinks. They were then randomized to receive oral melatonin, 3 mg/d (General Nutrition Corporation), or placebo (Standard Chem & Pharm Co, Ltd) at bedtime for 4 weeks. After a 2-week washout period, participants crossed to the alternate treatment. The study medication served as an add-on therapy to each patient's original treatments for AD, which were maintained to be the same throughout the study period. Visits occurred at the start of the trial (screening) and on the first and last day of each treatment period, during which AD disease severity was assessed, blood and urine samples were collected, questionnaires evaluating subjective symptoms were filled out, and pill count and adverse events were recorded. Severity of AD was assessed using the Scoring Atopic Dermatitis (SCORAD) index (range, 1-103, with greater scores indicating worse symptoms)[18] by the same physician (Y.-S.C.) blinded to the treatment randomization. The SCORAD index includes subjective visual analog scale scores from 0 to 10 (with greater numbers indicating worse symptoms) for degree of pruritus and sleep loss, which are referred to as the *pruritus score* and the *subjective sleep score*, respectively, in this study. The objective SCORAD index,[19] which excludes the SCORAD score for subjective symptoms (range, 0-83,

Figure 1. CONSORT Diagram of the Randomization and Follow-up of the Study Participants



with greater scores indicating worse symptoms), was also used for analysis. Sleep was evaluated by actigraphy (Mini-Mitter Actiwatch; Philips-Respironics). Each participant wore the actigraphic device on the nondominant wrist for 3 consecutive nights starting 3 nights before each treatment period and for the last 3 nights of each treatment period. In a subgroup of patients who offered consent, polysomnography was performed on the night before the first day and on the last night of each treatment period. The first urine sample on the morning after each actigraphic examination was obtained. Levels of urinary 6-sulfatoxymelatonin were assayed by enzyme-linked immunosorbent assay with a commercialized kit (IBL International GmbH) and were used to represent the melatonin level throughout the previous night.[20,21] A peripheral blood sample was taken from each participant at 9 AM on the morning after the last night of the sleep examination and stored at −80°C until measurements were performed. The serum total IgE level and levels of allergen-specific IgE to *Dermatophagoides pteronyssinus* (Derp), *Dermatophagoides farinae* (Derf), *Staphylococcus aureus* enterotoxin A, and *S aureus* enterotoxin B were measured with a fluorescence enzyme immunoassay (ImmunoCAP; Phadia AB). Allergen-specific IgE levels higher than 0.35 kU/L were defined as positive.

Outcomes

The primary study outcome was the SCORAD index for the evaluation of AD severity. Secondary outcomes included the objective sleep variables measured by actigraphy, the patient's subjective description of the change in sleep and dermatitis severity, the sleep variables measured by polysomnography, nocturnal urinary levels of 6-sulfatoxymelatonin, and serum total and allergen-specific IgE levels. Definitions of the sleep variables recorded in this study are described in eTable 1 in Supplement 2.

Statistical Analysis

Data were analyzed from January 27 to April 25, 2014. Efficacy analyses were conducted by modified intention to treat, excluding the patients who withdrew consent within 1 week after randomization. We used linear mixed-effects models to compare the mean change in outcomes after vs before treatment between the melatonin and placebo phases. The model included an indicator variable for phase (melatonin or placebo), time (before or after treatment), phase × time interaction, sequence (melatonin first or placebo first), and period (before or after the crossover). We adjusted for age and sex as potential confounders. Patient-specific random intercepts were used to account for the correlation owing to repeated measures. A *carryover effect* was defined as a statistically significant sequence effect. Owing to the relatively small sample size, we also performed the Wilcoxon signed rank test as a sensitivity analysis to compare the difference of each outcome measure before and after treatment between melatonin and placebo. The Wilcoxon signed rank test was also used for subgroup analyses. We used the McNemar test to analyze binary outcomes. For sample size calculation, we considered a SCORAD index decrease of 5.0 to be significant, and with the assumption that the SD is 10, we needed 32 patients to achieve 80% power at $\alpha = .05$. Assuming a withdrawal rate of 33%, we randomized a total of 48 patients. Statistical analyses were

Table 1. Baseline Characteristics of the Patients at Randomization

Characteristic	All Patients (N = 48)	Patients by Treatment Group[a]	
		Melatonin (n = 24)	Placebo (n = 24)
Female, No. (%)	23 (48)	13 (54)	10 (42)
Age, y	7.5 (3.7)	7.6 (4)	7.3 (3.5)
SCORAD index[b]	47.3 (22.7)	48.0 (24.9)	46.6 (20.7)
Objective SCORAD index[c]	37.0 (21.3)	38.7 (22.8)	35.2 (20.1)
Pruritus score[d]	5.6 (2.3)	5.0 (2.4)	6.3 (2.0)
Subjective sleep loss score[d]	4.7 (2.8)	4.3 (2.4)	5.1 (3.1)
Sleep-onset latency, min	36.5 (39.9)	41.8 (42.7)	31.4 (37.2)
Sleep efficiency, %	77.4 (12.0)	75.3 (12.3)	79.3 (11.7)
WASO, min	74.2 (44.5)	73.5 (41.8)	74.9 (47.8)
Wake in sleep interval, %	15.2 (9.2)	16.1 (9.7)	14.4 (8.8)
Total sleep time, min/night	415.8 (81.0)	393.0 (88.1)	437.7 (68.3)
Mobility in sleep, %	10.6 (6.9)	11.6 (7.9)	9.6 (5.9)
Fragmentation index[e]	15.6 (8.7)	17.3 (9.2)	14.0 (8.1)
Serum IgE level, kU/L	2130.5 (3222.9)	1882.6 (2451.7)	2389.7 (3915.2)
Urinary 6-sulfatoxymelatonin level, ng/mL	53.5 (62.7)	54.0 (66.0)	52.9 (61.1)

Abbreviations: SCORAD, Scoring Atopic Dermatitis; WASO, wake after sleep onset.

[a] Determined by which treatment was received first. Unless otherwise indicated, data are expressed as mean (SD). For all between-group comparisons, $P > .05$.

[b] Scores range from 0 to 103, with greater scores indicating worse symptoms.

[c] Scores range from 0 to 83, with greater scores indicating worse symptoms.

[d] Scores range from 0 to 10, with greater scores indicating worse symptoms.

[e] Greater scores indicate more fragmented sleep.

performed with SAS software (version 9.3; SAS Institute Inc). All the tests were 2 sided with an α level of .05.

Results

We recruited 73 children with AD from August 1, 2012, through January 31, 2013. After exclusion, 48 patients underwent randomization (median age, 7 years; age range, 1.8-17.1 years). Baseline demographic and clinical characteristics are detailed in **Table 1**. Withdrawals all occurred during the first treatment period (6 patients from the melatonin group and 4 from the placebo group). Reasons for withdrawal were similar between groups. Of the 38 patients undergoing evaluation by modified intention to treat, 18 were randomized to the melatonin phase first, and 20 were randomized to the placebo phase first (Figure 1).

Regarding AD severity, we found that the melatonin group had a greater decrease in the mean (SD) SCORAD index than the placebo group in the first treatment period (from 49.5 [25.7] to 42.3 [21.6] vs from 49.0 [21.6] to 48.8 [20.2]) and the second treatment period (from 48.7 [23.6] to 38.3 [20.7] vs from 46.8 [22.8] to 44.6 [20.5]) (eTable 2 in Supplement 2). The linear mixed-effects model showed that after adjusting for age and sex, melatonin treatment resulted in a decrease of the SCORAD index by 9.1 compared with placebo (95% CI, −13.7 to −4.6; $P < .001$) (**Table 2**). We found no significant carryover effect ($P = .67$) (**Figure 2**B and eTable 3 in Supplement 2). The period effect was significant ($P = .009$). Melatonin treatment also resulted in a decrease of the objective SCORAD index by 8.7 compared with placebo (95% CI, −12.6 to −4.8; $P < .001$) (Table 2), with no significant carryover effect ($P = .81$) and a significant period effect ($P = .02$) (eTable 3 in Supplement 2). The Wilcoxon signed rank test yielded results consistent with the linear mixed-effects model (Table 2 and Figure 2A and C).

Evaluation of sleep variables measured by actigraphy showed that the melatonin group had a greater decrease in the sleep-onset latency than the placebo group in the first (from 42.8 [48.5] to 24.4 [17.6] minutes vs 34.5 [31.0] to 22.9 [16.5] minutes) and the second (from 46.7 [31.3] to19.1 [22.8] minutes vs 27.9 [25.3] to 37.5 [28.7] minutes) treatment periods (eTable 2 in Supplement 2). The linear mixed-effects model showed that after adjusting for age and sex, melatonin treatment resulted in a decrease of the sleep-onset latency by 21.4 minutes more than placebo (95% CI, −38.6 to −4.2; $P = .02$) (Table 2). We found no significant carryover effect or period effect (eTable 3 in Supplement 2). The effect on the other sleep variables measured by actigraphy did not differ significantly between the melatonin and placebo phases (Table 2). The results from the Wilcoxon signed rank test arrived at the same conclusions (Table 2 and Figure 2D). The reduction in the sleep-onset latency did not correlate significantly with the degree of improvement in the SCORAD index with melatonin treatment ($r = −0.04$; $P = .85$).

More patients subjectively believed that their dermatitis had improved after melatonin treatment compared with placebo (17 of 36 [47%] vs 12 of 38 [32%]), and more patients believed that their sleep had improved after melatonin treatment compared with placebo (17 of 37 [46%] vs 13 of 38 [34%]), but neither difference reached statistical significance ($P = .20$ and $P = .30$, respectively; eTable 4 in Supplement 2). Thirteen patients underwent polysomnography in addition to actigraphy. Melatonin and placebo treatment did not have a significantly different effect on the stages of sleep and limb movement ($P > .05$).

Nocturnal urinary 6-sulfatoxymelatonin levels significantly increased after treatment with melatonin compared with placebo ($P < .001$). We found no significant difference between the effects of melatonin and placebo on total IgE level or on allergen-specific IgE levels to Derp, Derf, or *S aureus*

Table 2. Effects of Melatonin vs Placebo

Measure	Results by Study Phase, Mean (SD)						Difference of Treatment Effect From the Linear Mixed-Effects Model[a]		
	Melatonin			Placebo					
	Before	After	Difference	Before	After	Difference	Mean (95% CI)	*P* Value	*P* Value[b]
SCORAD index[c]	49.1 (24.3)	40.2 (20.9)	−9.9 (7.6)	48.0 (21.9)	46.8 (20.2)	−0.7 (8.6)	−9.1 (−13.7 to −4.6)	<.001	<.001
Objective SCORAD index[d]	38.6 (22.1)	31.3 (19.2)	−8.2 (7.2)	37.4 (20.8)	37.6 (19.4)	−0.6 (6.3)	−8.7 (−12.6 to −4.8)	<.001	<.001
Pruritus score[e]	5.6 (2.5)	5.1 (2.5)	−0.6 (2.0)	5.7 (2.1)	5.1 (2.4)	−0.5 (2.9)	0.0 (−1.2 to 1.2)	.99	.70
Subjective sleep score[e]	4.8 (2.7)	3.8 (2.4)	−1.1 (2.5)	4.9 (2.6)	4.1 (2.5)	−0.7 (2.8)	−0.4 (−1.6 to 0.9)	.57	.54
Sleep-onset latency, min	44.9 (39.5)	21.6 (20.4)	−23.4 (36.1)	31.5 (28.3)	29.6 (23.8)	−1.2 (31.5)	−21.4 (−38.6 to −4.2)	.02	.005
Sleep efficiency, %	74.4 (12.5)	76.7 (12.8)	2.4 (13.0)	78.0 (11.0)	77.7 (10.1)	0.6 (9.2)	2.2 (−3.1 to 7.4)	.41	.74
WASO, min	83.6 (63.8)	74.5 (53.5)	−9.0 (68.5)	74.0 (53.5)	75.9 (46.9)	−2.3 (38.1)	−8.2 (−31.9 to 15.4)	.49	.91
Wake in sleep interval, %	17.6 (11.6)	15.6 (10.7)	−2.1 (13.1)	14.8 (10.3)	15.7 (9.7)	−0.2 (7.4)	−2.3 (−6.8 to 2.3)	.33	.59
Total sleep time, min/night	380.1 (87.0)	390.1 (73.8)	10.0 (80.3)	410.5 (73.0)	391.7 (89.2)	−10.5 (88.2)	24.8 (−14.5 to 64.2)	.21	.20
Mobility in sleep, %	11.6 (7.3)	9.7 (4.7)	−2.0 (7.6)	9.5 (4.0)	10.4 (4.6)	0.9 (4.4)	−2.9 (−5.9 to 0.0)	.05	.21
Fragmentation index[f]	16.0 (7.8)	13.6 (5.8)	−2.4 (9.2)	14.7 (5.5)	15.3 (6.6)	0.7 (6.9)	−3.2 (−6.8 to 0.5)	.09	.40
IgE level, kU/L	2337.2 (3327.5)	2483.8 (3685.2)	108.4 (463.2)	2457.1 (3585.3)	2755.9 (4184.6)	243.6 (900.7)	−113.6 (−511.2 to 283.9)	.57	.56

Abbreviations: SCORAD, Scoring Atopic Dermatitis; WASO, wake after sleep onset.

[a] Estimated difference of the effect of melatonin vs placebo by the linear mixed model, adjusted for age and sex (coefficient of the phase × time interaction term).

[b] Comparisons of the absolute difference from baseline after melatonin and placebo treatment by the Wilcoxon signed rank test.

[c] Scores range from 0 to 103, with greater scores indicating worse symptoms.

[d] Scores range from 0 to 83, with greater scores indicating worse symptoms.

[e] Scores range from 0 to 10, with greater scores indicating worse symptoms.

[f] Greater scores indicate more fragmented sleep.

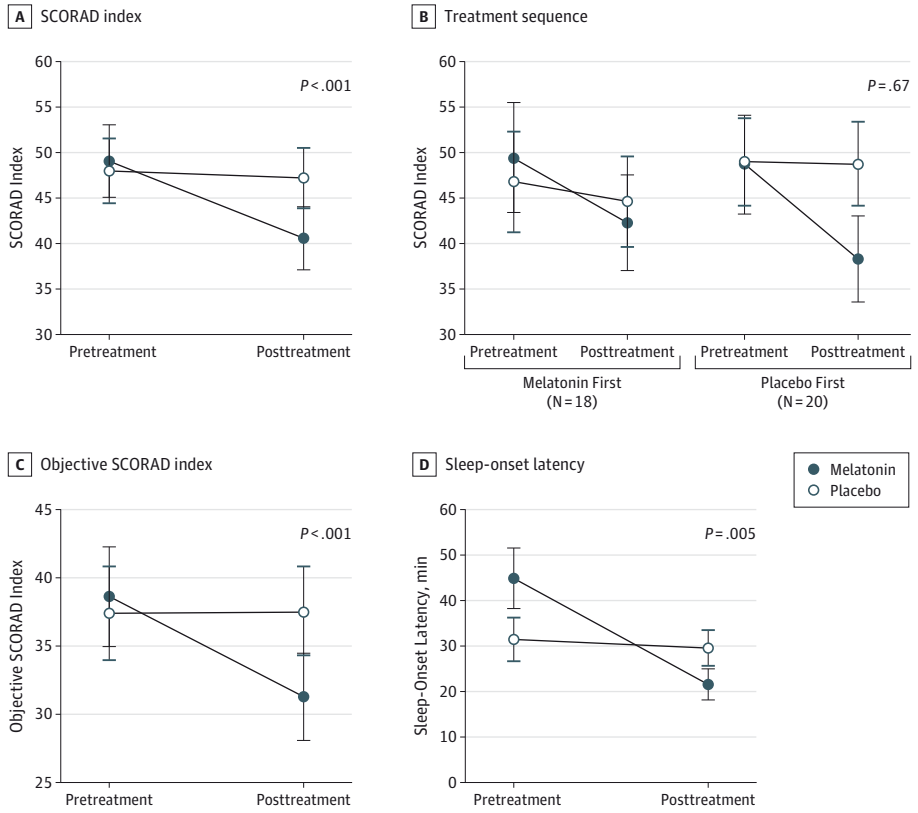
enterotoxins A or B ($P > .05$). No adverse effect of medication was reported throughout the study.

Discussion

Our study found that oral melatonin significantly improved the sleep-onset latency and disease severity in children and adolescents with AD. Although the magnitude of the effect is not great, many patients might benefit from this dual effect. Sleep disturbance is highly prevalent in children with AD and is a troubling problem that leads to impaired quality of life for the patients and their families.[2,3] A previous study[7] found that children with AD had significantly reduced sleep efficiency, longer sleep-onset latency, more sleep fragmentation, and less non-rapid eye movement sleep compared with healthy control individuals. In addition, sleep disturbance in children with AD was associated with scratching movements, greater severity of dermatitis, and reduced nocturnal melatonin secretion.[7] Worse sleep increases the likelihood that these children will scratch, which will further exacerbate the skin inflammation and lead to increased severity of skin disease. We hypothesized that melatonin, with its sleep-promoting and anti-inflammatory properties, could break this vicious cycle.

Our study found that melatonin significantly shortens sleep-onset latency by a mean of 23.4 minutes (52.1%). This magnitude of effect is comparable to melatonin's effect on children with attention-deficit/hyperactivity disorders or neurodevelopmental disabilities with impaired sleep onset.[22-24] Few studies have examined the efficacy of somnolent therapies for patients with AD, and trials in the pediatric population are especially lacking.[25] Clinicians wishing to target the disturbed sleep of patients with AD mostly rely on conventional experience or expert opinion with limited evidence.[25] First-generation antihistamines are traditionally used for sleep problems in patients with AD because they can antagonize the inflammatory effects of histamine released from mast cells and basophils and can cross the blood-brain barrier and thereby affect histamine's role in maintaining central nervous system arousal, which results in a sedating effect.[25] However, tolerance often occurs after 4 to 7 days of treatment and the sedating effect vanishes, limiting its usefulness.[26,27] Anticholinergic adverse effects, such as blurred vision and dry mouth, are also major concerns. Benzodiazepines have sedating and anxiolytic effects, but they carry the risks for tolerance to sedating effects, rebound worsening of sleep problems at discontinuation, and addiction. Negative adverse effects, including muscle relaxation and memory problems, also make them less favorable for use in children.[25] Chloral hydrate and clonidine have also been used, but supporting evidence was limited.[25] Melatonin has a good safety profile and has been suggested for the management of sleep problems in AD; however, no randomized clinical trial had been performed.[15,25] Our study is the first, to our knowledge, to use a validated objective measuring tool[7] to show evidence of improvement of sleep by melatonin supplementation in children with AD.

Figure 2. Severity of Atopic Dermatitis and Sleep-Onset Latency Before and After Melatonin Treatment



Data are expressed as both patient groups combined. A, The mean Scoring Atopic Dermatitis (SCORAD) index decreased significantly after melatonin treatment compared with placebo. B, The treatment sequence (melatonin first vs placebo first) did not result in a significant difference in the treatment effect. C, The mean objective SCORAD index decreased significantly after melatonin treatment compared with placebo. D, The mean sleep-onset latency decreased significantly after melatonin treatment compared with placebo. Error bars indicate standard errors. The SCORAD index ranges from 0 to 103, and the objective SCORAD index ranges from 0 to 83, with greater scores indicating worse symptoms.

Melatonin significantly improved AD severity by a mean reduction of the SCORAD index by 9.9 in 4 weeks. To avoid confounding by the patient's subjective scores of pruritus and sleeplessness, the objective SCORAD index, which represents the degree of severity based on the skin, was also analyzed, and results still showed that melatonin had an improving effect. Melatonin might help to reduce excessive scratching before sleep onset, a common clinical complaint in patients with AD, and therefore aid improvement in the skin inflammation by breaking the itch-scratch cycle. However, we found no significant correlation between improvement in the SCORAD index and reduction in the sleep-onset latency. Furthermore, melatonin did not improve the sleep variables other than sleep-onset latency, including sleep efficiency, mobile percentage in sleep, sleep fragmentation, and sleep architecture. Therefore, the effect of melatonin on AD might not be totally attributable to its effect on sleep but instead through its immunomodulatory or antioxidative properties. Various immunomodulatory mechanisms of melatonin have been reported. Helper T cells T_H1 and T_H2 express membrane and nuclear receptors for melatonin. Via these receptors, melatonin induces the synthesis of interferon-γ, interleukin 2 (IL-2), IL-6, and IL-12 by lymphocytic and monocytic cell lines; amplifies melatonin receptors; and alters the balance of T_H1 and T_H2 cells mainly toward T_H1 responses.[15,28,29] Melatonin also influences the activity of natural killer cells, T and B lymphocytes, granulocytes, monocytes, and mast cells.[15,30] Furthermore, through the upregulation of antioxidant enzymes, melatonin efficiently neutralizes several free radicals and stabilizes cell membranes.[31] In addition, melatonin might have a role in the pathophysiological mechanism of AD.[7,32] Cikler et al[33] found that long-term melatonin treatment of stress-induced skin disorders in an experimental rat model reduced infiltration and activation of mast cells in the dermis. Kim et al[34] found that melatonin suppressed the development of AD-like dermatitis in NC/Nga mice by reducing the total serum IgE level and production of IL-4 and interferon-γ by activated $CD4^+$ T cells. Our study is the first, to our knowledge, to find that melatonin could improve AD severity in humans. However, we found no significant change in the serum total or allergen-specific IgE levels after melatonin treatment in our study. Whether and how melatonin modulates the complex inflammatory pathways in AD is an interesting field to explore in future studies.

We found no significant carryover effect from the crossover study design. However, the period effect was significant for the SCORAD index and the objective SCORAD index, demonstrating that melatonin improved disease severity significantly more in the second than in the first treatment period. This result might have occurred because the participants became more familiar with the study protocol and thus exhibited better adherence in the second treatment period, and they might have established more stable

methods of skin care and sleep hygiene as the trial progressed, and thereby more effectively demonstrating the influence of melatonin. This finding supports a true effect of melatonin on improvement of dermatitis severity in children with AD.

As expected, a high dropout rate occurred in our study. Most of the dropouts resulted from withdrawal of consent because family members other than the parent who gave consent found out about the study and decided against it. This consequence reflects the general concern of family members about giving a child medication for sleep. One attractive property of melatonin is that it is safe with minimal adverse effects and does not have addictive or withdrawal concerns.[9] A meta-analysis found that the most commonly reported adverse effects of melatonin included drowsiness, dizziness, nausea, and headaches, but the occurrence of these events did not differ significantly between melatonin and placebo.[9] No adverse event was reported throughout our study.

This study has some limitations. Only a small subgroup of patients received the polysomnographic examination, so we might not have had enough statistical power to detect an effect of melatonin on the sleep architecture. In addition, owing to our relatively small sample size, we could not investigate whether the treatment effect of melatonin differs between subgroups of patients with different ages or initial disease severity. However, the improvement in sleep-onset latency and dermatitis severity after melatonin treatment reached statistical significance despite our small sample size, which reflects the substantiality of the effect. Finally, further studies are needed to evaluate the optimal dose and duration of melatonin treatment for these patients.

Conclusions

Melatonin significantly improved the severity of dermatitis and reduced sleep-onset latency in children with AD and sleep disturbance. We recommend melatonin supplementation for these patients because it is a potentially safe and effective way to improve their sleep and skin condition simultaneously.

ARTICLE INFORMATION

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