

# Atopic Dermatitis, Melatonin, and Sleep Disturbance

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## KEY WORDS

sleep disturbance, atopic dermatitis, actigraphy, polysomnography, SCORAD, melatonin, IgE, dust mite, staphylococcal enterotoxin

## ABBREVIATIONS

AD—atopic dermatitis  
Derf—*Dermatophagoides farinae*  
Derp—*Dermatophagoides pteronyssinus*  
IFN—interferon  
IgE—immunoglobulin E  
IL—interleukin  
NREM—nonrapid eye movement  
PSG—polysomnography  
SCORAD—Scoring Atopic Dermatitis  
SEA—*Staphylococcus aureus* enterotoxin A  
SEB—*Staphylococcus aureus* enterotoxin B

Dr Chiang conceptualized and designed the study, and reviewed and revised the manuscript; Dr Chang designed and carried out the study, did the data analysis, and drafted the initial manuscript; Drs Lee, Chen, Lee, and Sun modified the study design, coordinated and supervised the study, and reviewed and revised the manuscript; Drs Chou, Dai, Lin, Wang, Yu, Yang, and Wan coordinated and supervised patient recruitment and data collection and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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**WHAT'S KNOWN ON THIS SUBJECT:** Sleep disturbance affects 47% to 60% of children with atopic dermatitis and is a leading cause of impaired quality of life for the patients and their family.



**WHAT THIS STUDY ADDS:** Sleep disturbance in children with atopic dermatitis can be predicted by a Scoring Atopic Dermatitis index of  $\geq 48.7$ , and lower nocturnal melatonin secretion might play a role in the pathophysiology.

## abstract



**BACKGROUND AND OBJECTIVES:** Sleep disturbance is common in patients with atopic dermatitis (AD). However, studies have largely been questionnaire-based, and the pathophysiology remains unclear. The aims of this study were to determine objective characteristics of sleep disturbance in children with AD and explore contributing factors and clinical predictors.

**METHODS:** Sleep parameters were measured by actigraphy and polysomnography in 72 patients with AD and 32 controls ages 1 to 18 years. Urinary 6-sulfatoxymelatonin levels, serum cytokines, and total and allergen-specific immunoglobulin E (IgE) levels were also measured.

**RESULTS:** The patients with AD had significantly reduced sleep efficiency, longer sleep onset latency, more sleep fragmentation, and less nonrapid eye movement sleep. Results from actigraphy correlated well with those from polysomnography. The AD disease severity was associated with sleep disturbance ( $r = 0.55-0.7$ ), and a Scoring Atopic Dermatitis index of  $\geq 48.7$  predicted poor sleep efficiency with a sensitivity of 83.3% and a specificity of 75% (area under the curve = 0.81,  $P = .001$ ). Lower nocturnal melatonin secretion was significantly associated with sleep disturbance in the patients with AD. Other correlates of sleep disturbance included pruritus, scratching movements, higher total serum IgE levels, and allergic sensitization to dust mite and staphylococcal enterotoxins.

**CONCLUSIONS:** Poor sleep efficiency is common in children with AD and can be predicted by the Scoring Atopic Dermatitis index. Melatonin and IgE might play a role in the sleep disturbance. Further studies are required to explore the mechanisms and clinical implications, and actigraphy could serve as a useful evaluating tool. *Pediatrics* 2014;134:e397-e405

Atopic dermatitis (AD) is a common chronically relapsing pruritic inflammatory skin disease.<sup>1</sup> Disturbed sleep is frequently reported by the patients and their family and is a major factor leading to an impaired quality of life.<sup>2-4</sup> Sleep disturbance can have many negative consequences, including impaired neurocognitive function, higher rates of behavioral problems, and changes in mood.<sup>5,6</sup> Therefore, the recognition and proper management of sleep disturbance should be an important issue in AD.

The sleep disturbance in AD might be due to the pruritus and scratching movements during sleep,<sup>7-10</sup> but it is likely that other factors are involved.<sup>11</sup> Melatonin is a hormone secreted by the pineal gland that is essential for regulating the circadian rhythm.<sup>12</sup> Dysfunction in the diurnal secretion of melatonin in patients with AD has been reported,<sup>13</sup> but its association with their sleep disturbance has not been studied. Despite an increasing recognition of the prevalence and negative effects of sleep problems in patients with AD, the pathophysiology of this sleep disturbance is still unclear, and little is known about how to identify those at high risk for sleep disturbance. This study aimed to objectively measure and determine the characteristics of sleep disturbance in children with AD, and to explore the possible contributing factors to guide further clinical management.

## METHODS

### Participants

Patients with physician-diagnosed AD involving at least 5% of the total body surface area, aged between 1 and 18 years, were recruited from the outpatient department of the National Taiwan University Hospital between May 2011 and January 2013. Healthy volunteers in the same age group served as controls. Exclusion criteria included the

following: having documented sleep disorders, neuropsychiatric disorders, or having taken medication for insomnia or antidepressants within 4 weeks before the baseline visit. AD disease severity was assessed by the same physician by using the Scoring Atopic Dermatitis (SCORAD) index.<sup>14</sup> The SCORAD index includes a subjective visual analog scale score from 0 to 10 for degree of pruritus, which is referred to as the pruritus score in this study. The "objective SCORAD,"<sup>15</sup> which excludes the score for subjective symptoms in the SCORAD index, was also used for analysis.

All study participants and their parents provided written informed consent, and the institutional review committee of National Taiwan University Hospital approved the study protocol. This study conformed to the principles of the Helsinki Declaration.

### Subjective Symptoms of Sleep Disturbance

The participants and their parents/main caregivers completed a questionnaire to evaluate their subjective symptoms of sleep disturbance. The questions included problems with sleep initiation (taking >30 minutes to fall asleep) or maintenance (waking up for at least 1 time per night), difficulty falling asleep after waking up at night, or difficulty waking up in the morning.

### Objective Measurements of Sleep by Actigraphy and Polysomnography

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. Then objective sleep parameters were measured by actigraphy (Mini-Mitter Actiwatch Score, Philips-Respironics, Bend, OR). Each participant wore the actigraph on his/her nondominant wrist during the night

of the study. Definitions of the sleep parameters recorded in this study are described in Supplemental Table 4. In patients with AD, poor sleep efficiency was defined as sleep efficiency lower than 2 SDs from the mean of the healthy controls. In a random subgroup of patients and controls, a polysomnography (PSG) study was performed at the Center of Sleep Disorders of the National Taiwan University Hospital on the same night of the actigraphy study by using standard procedures.<sup>16</sup> Those who did not have the PSG study had the actigraphy study at home. Because of administrative reasons, PSG recordings were terminated at 6 AM, while actigraphy studies were recorded until the patient got up to be comparable for all the participants.

### Evaluations of Melatonin and Cytokines

The first urine sample in the morning after the actigraphy examination was obtained. The urinary 6-sulfatoxymelatonin levels were assayed by enzyme-linked immunosorbent assay with a commercialized kit (IBL International GmbH, Germany), and were used to represent the level of melatonin secretion throughout the previous night.<sup>17-19</sup> A peripheral blood sample was taken from each participant at 9 AM on the morning after the sleep examination, and the sera were stored at -80°C until the biomarker measurements. The serum levels of interleukin (IL)-31, interferon- $\gamma$  (IFN- $\gamma$ ), serotonin, IL-10, IL-6, IL-4, and IL-1 $\beta$  were measured by enzyme-linked immunosorbent assay with commercially available kits (Genway Biotech, San Diego, CA, for serotonin; R&D Systems, Minneapolis, MN, for all other cytokines). The serum total immunoglobulin E (IgE) level and allergen-specific IgE levels to dust mites *Dermatophagoides pteronyssinus* (Derp) and *Dermatophagoides farinae* (Dermf), *Staphylococcus aureus* enterotoxin A (SEA), and *Staphylococcus aureus*

enterotoxin B (SEB) were measured with the ImmunoCAP fluorescence enzyme immunoassay (Phadia AB, Sweden). Specific IgE levels  $>0.35$  kU/L were defined as positive.

### Statistical Analysis

The  $\chi^2$  test or the Student's *t* test was used to compare the data between the patients with AD and controls or between the patient subgroups. The Mann-Whitney *U* test was used if the case number in any subgroup was  $<30$ . Correlation analyses were performed by using general linear models. For participants who had urine voiding in the middle of the night, the morning urinary 6-sulfatoxymelatonin data were excluded. All statistical analyses were performed by using SPSS (version 15.0; SPSS, Inc, Chicago, IL).  $P < .05$  defines statistical significance.

## RESULTS

Seventy-two patients with AD and 32 healthy controls were enrolled. There was no significant difference in the age or gender between these 2 groups (Table 1). Fifty-three of the AD patients and 20 controls received a PSG examination in addition to the actigraphy study. In patients with AD, the SCORAD index was  $41.3 \pm 22.1$ , ranging from 6.7 to 89.7.

### Subjective and Objective Measurements of Sleep Disturbance

The questionnaire results (Supplemental Table 5) revealed that subjective sleep quality was poor in 54.2% of the patients with AD compared with 6.2% of the controls ( $P < .001$ ). Difficulty falling asleep, difficulty awakening in the morning, and sleepiness in the daytime were all common in AD. The total time in bed and sleep onset latency were both longer, and there were more awakenings at night in the patients with AD.

The actigraphy results revealed that the patients with AD had lower sleep efficiency compared with the controls (Table 1). They also had longer sleep onset latency and more sleep fragmentation (Table 1). The PSG results additionally revealed that the patients with AD had significantly less nonrapid eye movement (NREM) sleep than the controls (Table 2). The sleep parameters measured by actigraphy had good correlation with those measured by PSG ( $r = 0.67-0.76$ ,  $P < .001$ , Supplemental Table 6).

### Disease Severity and Sleep Disturbance

The correlation analyses revealed that a higher SCORAD index was significantly

associated with a lower sleep efficiency ( $r = -0.55$ ,  $P < .001$ ), shorter total sleep time ( $r = -0.29$ ,  $P = .017$ ), longer wake after sleep onset ( $r = 0.62$ ,  $P < .001$ ), higher Wake% ( $r = 0.69$ ,  $P < .001$ ), and more sleep fragmentation ( $r = 0.70$ ,  $P < .001$ ; Fig 1 A, B, and C). Analyses with the objective SCORAD index also revealed similar results (Fig 2 A, B, C, and D). Based on the receiver operating characteristic curve analysis, a SCORAD index  $\geq 48.7$  predicted poor sleep efficiency, with a sensitivity of 83.3% and a specificity of 75% (area under the curve = 0.81,  $P = .001$ ; Fig 3).

Subgroup analyses dividing patients with AD into those who had taken first generation antihistamines ( $n = 28$ ) and those who had not ( $n = 44$ ) revealed that none of the sleep parameters measured by actigraphy were significantly different between these 2 groups, and the association between SCORAD index and sleep disturbance was significant in both groups, with slightly higher correlation in the antihistamine group. (For correlation between SCORAD index and sleep efficiency:  $r = -0.65$ ,  $P < .001$  for those who had taken antihistamines, and  $r = -0.37$ ,  $P = .018$  for those who had not.)

### Itch and Scratch in Sleep Disturbance

There was significantly more movement during sleep in the patients with AD compared with the controls (Tables 1 and 2), and movement was highly correlated with the SCORAD index ( $r = 0.70$ ,  $P < .001$ ; Fig 1D) and sleep efficiency ( $r = -0.73$ ,  $P < .001$ ). Limb movement mostly occurred during the sleep stage N1 in the healthy controls, but there was more limb movement in the patients with AD during the deeper sleep stages N2 and N3 (Supplemental Fig 5).

The pruritus score was correlated with the objective SCORAD index ( $r = 0.54$ ,  $P < .001$ ) in the patients with AD and was also correlated with lower sleep efficiency

**TABLE 1** Demographic Data and Actigraphy Results in Patients and Controls

	Patients ( $n = 72$ )	Controls ( $n = 32$ )	<i>P</i>
Age, y	$7.5 \pm 3.9$	$8.6 \pm 3.9$	.19
Gender, male/female	36/36	17/15	.77
SCORAD index	$41.3 \pm 22.1$	—	—
Time in bed, min <sup>a</sup>	$526.3 \pm 57.9$	$487.7 \pm 78.0$	.021
Sleep efficiency, % <sup>b</sup>	$74.5 \pm 9.2$	$81.2 \pm 7.6$	.001
Total sleep time, min	$391.3 \pm 68.6$	$395.3 \pm 64.4$	.78
Wake after sleep onset, min <sup>b</sup>	$73.2 \pm 45.7$	$50.7 \pm 29.9$	.004
Wake% in sleep <sup>b</sup>	$15.4 \pm 8.2$	$11.2 \pm 5.9$	.005
Sleep onset latency, min <sup>b</sup>	$45.0 \pm 29.3$	$27.0 \pm 16.2$	$<.001$
Mobile% in sleep <sup>a</sup>	$11.1 \pm 6.7$	$8.2 \pm 4.6$	.031
Sleep fragmentation index <sup>b</sup>	$22.1 \pm 8.4$	$17.0 \pm 6.8$	.004

—, not available.

<sup>a</sup>  $P < .05$ .

<sup>b</sup>  $P < .01$ .

**TABLE 2** PSG Results in Patients and Controls

	Patients (n = 53)	Controls (n = 20)	P
Age, y	8.0 ± 4.2	9.5 ± 4.1	.16
Sleep efficiency, % <sup>a</sup>	84.5 ± 9.3	94.1 ± 7.5	<.001
Total sleep time, min	348.4 ± 42.8	371.8 ± 45.4	.05
Wake after sleep onset, min <sup>b</sup>	42.6 ± 39.8	22.7 ± 26.7	.019
Sleep stage N1, %	4.8 ± 3.8	4.4 ± 3.0	.681
Sleep stage N2, %	34.4 ± 14.3	33.8 ± 16.2	.883
Sleep stage N3, %	32.8 ± 14.8	38.1 ± 17.2	.203
NREM sleep total, % <sup>b</sup>	71.2 ± 9.44	76.2 ± 4.79	.004
Sleep stage REM, %	17.3 ± 6.2	17.9 ± 6.5	.734
Sleep stage W (wakefulness), % <sup>b</sup>	10.7 ± 9.6	5.9 ± 7.5	.032
Limb movement index, h <sup>a</sup>	13.0 ± 13.4	5.6 ± 2.9	<.001

REM, rapid eye movement.

<sup>a</sup> P < .01.<sup>b</sup> P < .05.

and more sleep fragmentation (Fig 2 E, F, G, and H).

### Nocturnal Melatonin Secretion in Relation to Sleep

Nocturnal melatonin levels were significantly higher in the patients with AD compared with the controls ( $P = .003$ ; Fig 4A). However, in the patients with AD, a higher nocturnal melatonin level was significantly correlated with better sleep

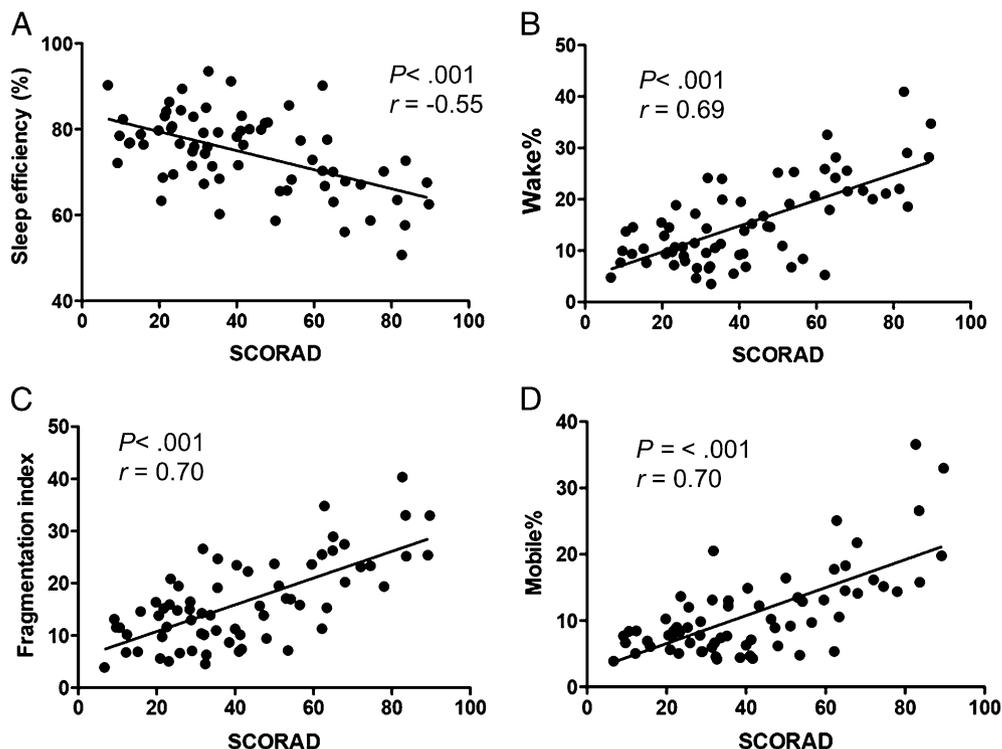
efficiency ( $r = 0.4$ ,  $P = .004$ ; Fig 4B), longer total sleep time ( $r = 0.38$ ,  $P = .005$ ), less sleep fragmentation ( $r = -0.34$ ,  $P = .016$ ), and a lower SCORAD index ( $r = -0.28$ ,  $P = .04$ ).

### Serum Total and Allergen-Specific IgE and Cytokines

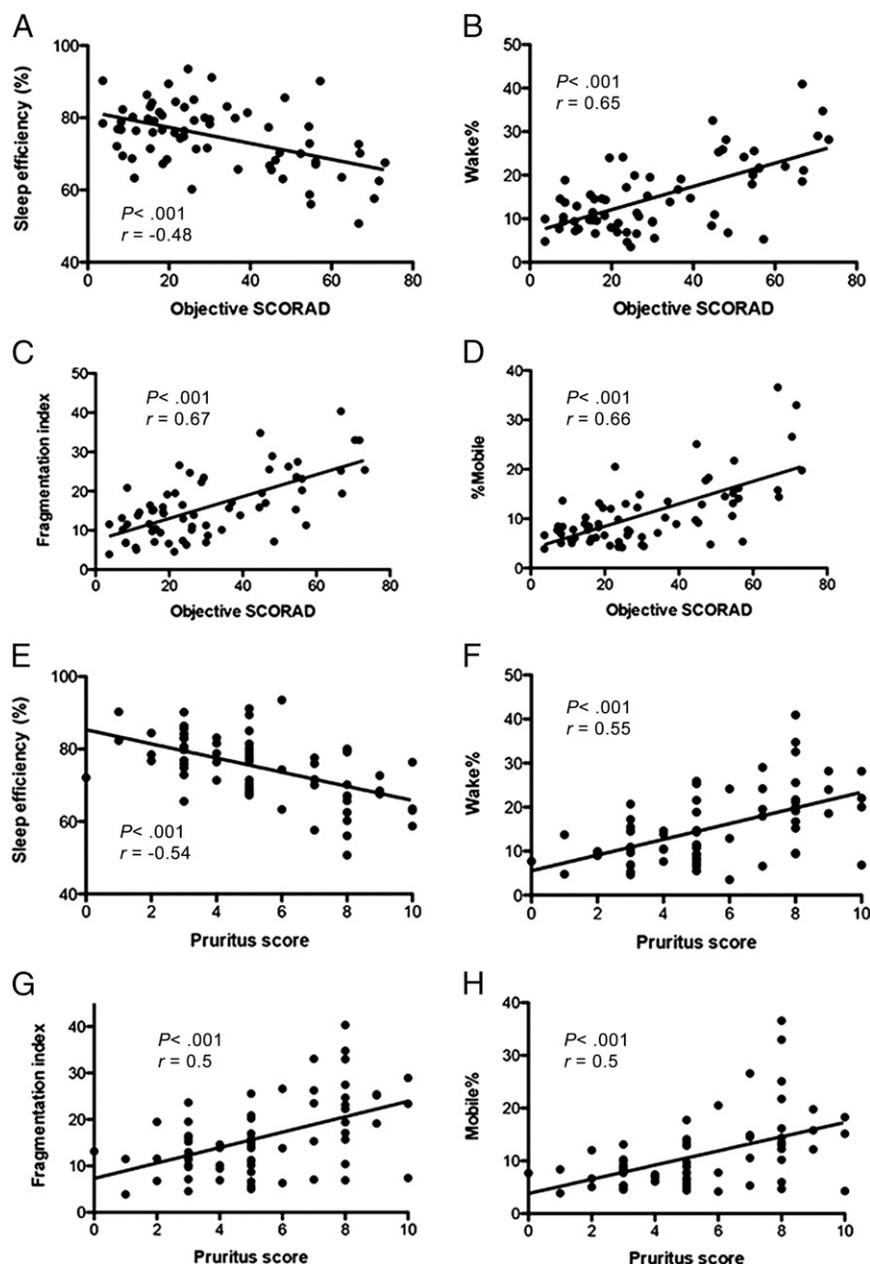
The serum total IgE levels in the patients with AD were significantly higher than in the controls ( $2308.0 \pm 3184.0$  vs

$39.1 \pm 36.5$  kU/L,  $P < .001$ ) and were correlated with the SCORAD index ( $r = 0.57$ ,  $P < .001$ ). In addition, the serum total IgE level and the Derp- and Derf-specific IgE levels were all significantly associated with sleep disturbance (Table 3). Those who were sensitized to SEA or SEB had more wakefulness in their sleep (Table 3). The pruritus score was significantly correlated with the serum total IgE levels ( $r = 0.53$ ,  $P < .001$ ) and the Derp and Derf-specific IgE levels. Those who were sensitized to SEA and SEB also had a higher pruritus score (Table 3).

In the patients with AD, a higher serum IL-4 level was weakly correlated with a higher sleep efficiency. The ratio of IFN- $\gamma$  and IL-4 (IFN- $\gamma$ :IL-4) was significantly lower in the subgroup of patients with poor sleep efficiency ( $P = .01$ ). Serum IL-31 level was correlated with a lower percentage of stage N1 sleep, and the serotonin level was correlated with a lower percentage of N1 sleep

**FIGURE 1**

Correlation of AD disease severity with sleep parameters. A higher SCORAD index is significantly associated with lower sleep efficiency (A), larger percentage of time awake in the sleep period (B), more sleep fragmentation (C), and more movement in sleep (D).



**FIGURE 2**

Correlation of an objective SCORAD index and pruritus score with sleep parameters. A higher objective SCORAD index (A–D) and higher pruritus score (E–H) are correlated with a lower sleep efficiency, more time awake in the sleep period, more sleep fragmentation, and more movement in sleep.

and a higher percentage of N3 sleep (Supplemental Table 7).

## DISCUSSION

Observational studies have revealed sleep disturbances in 47% to 60% of children with AD.<sup>20–22</sup> In our screening questionnaires, there was a subjective recognition of poor sleep quality in 54.2% of patients with AD. Difficulty falling

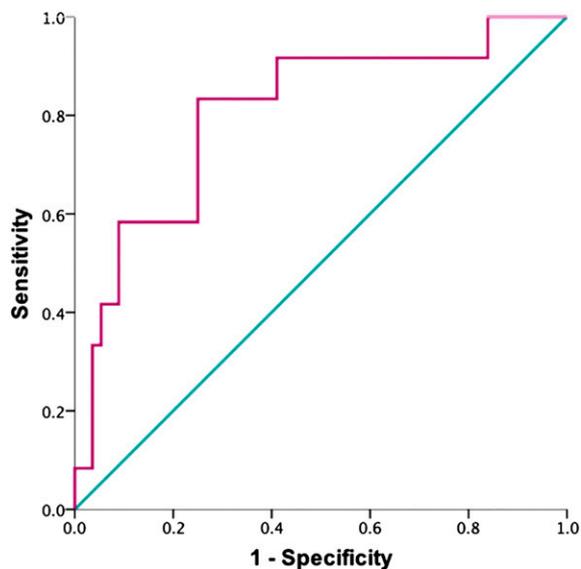
asleep, more nighttime awakenings, and difficulty awaking in the morning were generally noted in more than half of our patients with AD. These highly prevalent problems might not always be considered in routine clinical management.<sup>23</sup>

It has been found that the subjective perception of sleep quality did not necessarily match the objective measurements.<sup>24,25</sup> Therefore, we conducted

an objective analysis of sleep with PSG and actigraphy. PSG is regarded as the gold standard in sleep examinations, but it usually has to be performed in a sleep center, which could be inconvenient for many patients and their families. The different sleeping environments and the attachment of numerous leads and equipment to the patient in the PSG setting could also cause irritation of the skin or other discomfort for the patient with AD, and thus their home sleeping conditions might not be truly reflected. In contrast, actigraphy, a small, wrist-worn device that estimates sleep-wake patterns by using activity-based monitoring, has increasingly been used in recent years for delineating sleep patterns<sup>26,27</sup> because of its ease of use, especially for the pediatric population,<sup>25,28,29</sup> but its validation with PSG measurements in children with AD had not been established. Our study is the first to demonstrate a good correlation of results by actigraphy and PSG in this patient group, and we suggest that actigraphy is a good alternative for further sleep studies in children with AD.

Our actigraphy results confirmed the presence and depicted the characteristics of sleep disturbance in children with AD. They had lower sleep efficiency, it took them longer to fall asleep, there was more wakefulness after sleep onset, and the sleep was more fragmented. In addition, our PSG results revealed that the patients with AD had significantly less NREM sleep. The NREM sleep stage is important in conservation of brain energy and facilitates memory consolidation.<sup>30</sup> Whether shortened duration of NREM sleep would affect the memory or neurocognitive function in patients with AD should be explored in further studies.

We found that the AD disease severity is associated with sleep disturbances. A higher SCORAD index is significantly associated with a lower sleep efficiency and more fragmented sleep. To exclude



**FIGURE 3**

Receiver operating characteristic curve for predicting poor sleep efficiency by SCORAD index. The area under the receiver operating characteristic curve is 0.81,  $P = .001$ . A SCORAD index  $\geq 48.7$  predicted poor sleep efficiency, defined as sleep efficiency  $< 2$  SDs from the mean of the healthy controls, with a sensitivity of 83.3% and a specificity of 75%.

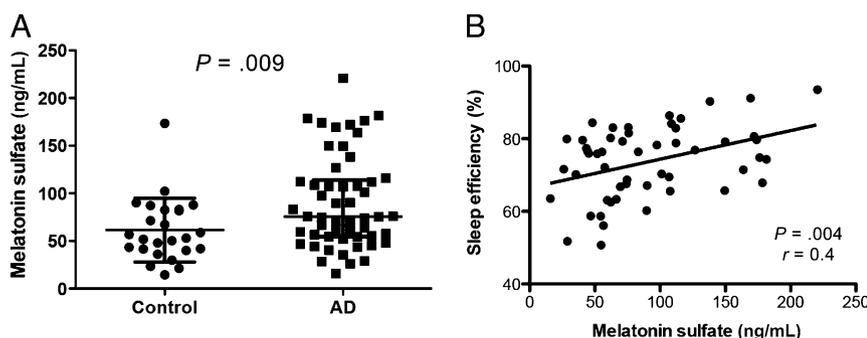
possible confounding by the subjective sleep loss score included in the SCORAD index, we further analyzed the objective SCORAD index and pruritus scores separately. Both individual scores remained significantly associated with sleep disturbance. This indicates that the severity of the skin inflammation and the level of pruritus might both contribute to the sleep problems. Furthermore, we identified a threshold value of SCORAD index  $\geq 48.7$  as a good predictor of poor sleep efficiency with high sensitivity and specificity. This could provide a simple

way for clinicians to promptly recognize patients with AD at high risk of sleep disturbance.

Previous studies have suggested that itch and scratching movements might be the cause of disturbed sleep in patients with AD.<sup>7-9,31</sup> Our study supports this with finding that more movements in sleep and a higher pruritus score were both associated with lower sleep efficiency. However, it is important to note that arousals caused by limb movement were not significantly correlated with sleep efficiency in our patients (data not

shown). A previous study also revealed that scratching accounted for only 15% of arousals in patients with AD.<sup>11</sup> Therefore, scratching movements play a part in the sleep disturbance of patients with AD, but are unlikely the sole etiology.

Melatonin is important in regulating sleep.<sup>12</sup> The sedative effect of melatonin might be due to its direct phase-shifting effect on the suprachiasmatic nucleus, the master controller of circadian rhythms in the body,<sup>32</sup> or its ability to decrease the core body temperature, which may induce sleepiness.<sup>33</sup> Melatonin also has immunomodulatory and antiinflammatory effects.<sup>34,35</sup> We found that nocturnal melatonin levels were significantly higher in the patients with AD compared with the controls. It is also our novel finding that in patients with AD, a higher nocturnal melatonin level was associated with better sleep efficiency, less sleep fragmentation, and milder disease severity. It has been reported that sleep deprivation could result in increased melatonin secretion.<sup>36,37</sup> Therefore, a potential explanation of our findings is that there is a compensatory mechanism to modulate the sleep disturbance in patients with AD, and those who respond to compensatorily increased melatonin secretion benefit from its effect in improving sleep and skin condition. It is also possible that melatonin plays a role in the pathogenesis of AD. Further studies are needed to support these hypotheses. Contrary to our results, a reduced morning serum melatonin level has been reported in AD.<sup>38</sup> However, previous studies have primarily measured serum melatonin levels in patients with AD,<sup>13,38</sup> but melatonin is secreted with a circadian rhythm in which serum levels peak between midnight and 3 AM, while the daytime levels are low.<sup>39</sup> This makes it difficult to make comparisons or draw conclusions from a serum sample at a single time point. We used



**FIGURE 4**

Nocturnal melatonin level in patients with AD and its association with sleep disturbance. Urinary 6-sulfatoxymelatonin levels in the first morning urine sample, representing nocturnal melatonin levels, were higher in the patients with AD compared with the controls (A), and a higher level is correlated with higher sleep efficiency (B).

**TABLE 3** Correlation of Total and Allergen-Specific IgE Levels With Sleep Parameters

Parameter	IgE		Derp		Derf		SEA			SEB		
	P	r	P	r	P	r	+	−	P	+	−	P
							(n = 20)	(n = 45)		(n = 28)	(n = 37)	
Time in bed, min	.151	—	.154	—	.105	—	525.97 ± 91.28	526.8 ± 65.31	.951	526.31 ± 60.78	526.74 ± 82.8	.842
Sleep onset latency, min	.652	—	.522	—	.369	—	39.56 ± 30.91	48.5 ± 28.21	.147	44.09 ± 31.65	47.01 ± 27.47	.5
Sleep efficiency, %	.002	−0.38	.054	—	.035	−0.27	71.23 ± 11.2	75.35 ± 7.97	.167	72.12 ± 9.38	75.61 ± 8.88	.204
WASO, min	.031	0.28	.106	—	.069	—	95.09 ± 52.66	66.16 ± 42.16	.031	90.85 ± 53.07	62.82 ± 38.5	.03
Wake%	.001	0.42	.006	0.34	.005	0.36	20.04 ± 9.42	13.79 ± 7.24	.015	18.78 ± 9.31	13.34 ± 6.89	.021
Total sleep time, min	.001	−0.4	.019	−0.3	.007	−0.34	374.83 ± 85.61	395.59 ± 55.74	.562	378.66 ± 59.12	397.38 ± 71.1	.233
Mobile %	.001	0.42	.01	0.33	.007	0.34	15.09 ± 8.81	9.87 ± 5.3	.011	13.2 ± 8.57	10.08 ± 5.03	.221
Fragmentation index	.002	0.38	.02	0.3	.011	0.32	20.86 ± 9.06	15 ± 7.35	.014	18.1 ± 9.8	15.72 ± 6.89	.466
SCORAD index	<.001	0.57	<.001	0.43	<.001	0.5	59.4 ± 23.6	35 ± 17.4	<.001	47.6 ± 24.4	38.5 ± 20.3	<.001
Objective SCORAD index	<.001	0.61	<.001	0.45	<.001	0.53	47.8 ± 20.3	25.5 ± 15.7	<.001	35.3 ± 20.9	29.7 ± 19.1	.361
Pruritus score	<.001	0.53	<.001	0.43	<.001	0.44	6.4 ± 2.7	4.9 ± 2.3	.025	6.5 ± 2.5	4.4 ± 2.1	.001

WASO, wake after sleep onset. —, r is not shown if  $P > .05$ .

morning urinary 6-sulfatoxymelatonin levels for better assessment of nocturnal melatonin secretion.<sup>40</sup> Our findings might suggest the potential use of exogenous melatonin treatment of patients with AD to improve sleep efficiency and skin inflammation.

The total serum IgE level has been reported to be associated with pruritus and sleep loss in patients with AD,<sup>10,41</sup> and whether it is associated with disease severity is controversial.<sup>10,41</sup> Our study revealed that the total IgE level was correlated with the objective SCORAD index and the pruritus score. In addition, a higher IgE level was associated with lower sleep efficiency, more wakefulness in sleep, and more sleep fragmentation. It is likely that the link between the IgE level and sleep disturbance is through its association with AD disease severity and pruritus. We also found that the levels of specific IgE to dust mite Derp and Derf were correlated with sleep disturbance. In Taiwan, dust mites are the most common allergens that induce allergic sensitization in children.<sup>42</sup> Pillows and mattresses are major reservoirs of dust mite allergens, so the sleeping environment is a main source of dust mite exposure. Our results suggest that environmental control measures against dust mite might help to improve the sleep disturbance in patients with AD. Colonization of the skin by *S*

*aureus* occurs in more than 90% of patients with AD, and *S aureus* enterotoxins can increase the skin inflammation.<sup>1</sup> We also found that patients sensitized to SEA or SEB have significantly more sleep disturbance. This might indicate that an intervention against *S aureus* colonization in those sensitized to SEA or SEB could potentially improve their sleep.

It is known that sleep has complex relationships with immune function and cytokine production.<sup>43,44</sup> Some studies have suggested that sleep loss is associated with a shift in the Th1/Th2 balance toward Th2 dominance.<sup>45</sup> Our data support this hypothesis because IFN- $\gamma$ :IL-4 was significantly lower in the subgroup of patients with AD with poor sleep efficiency. IL-31 is an inducer of pruritus found to be correlated with SCORAD index and subjective sleeplessness in children with AD.<sup>46</sup> We found that the serum levels of IL-31 and serotonin, another inducer of pruritus,<sup>47,48</sup> were associated with a change in sleep architecture. Further studies are warranted to substantiate these exploratory findings.

This study has some limitations. It is a cross-sectional study, so direct causal relationships among AD disease severity, IgE, melatonin, and sleep disturbance could not be established. Regarding our cytokine studies, serum cytokine levels

might fluctuate with the circadian rhythm,<sup>43</sup> so a single morning blood sample might not enable us to appreciate the full picture of the role of cytokines.

## CONCLUSIONS

Sleep disturbance is common in patients with AD, and is strongly associated with disease severity. A SCORAD index of  $\geq 48.7$  would predict poor sleep efficiency. Factors that might contribute to sleep disturbance include lower nocturnal melatonin secretion, pruritus, scratching movements, higher total serum IgE levels, and allergic sensitization to dust mite and Staphylococcal enterotoxins. We validated that actigraphy is a good tool to assess sleep in children with AD. We suggest a regular evaluation of sleep quality in children with AD and stress the importance of disease control in those with sleep disturbance. Our study also provides evidence supporting further research into potential pharmacological manipulation of sleep in patients with AD.

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