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# The relationship between sleep quality and chronotype differences and urticaria severity in patients with chronic spontaneous urticaria

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## Abstract

**Introduction:** Chronic spontaneous urticaria (CSU) is characterized by persistent or recurrent pruritic lesions that last more than 6 weeks. Patients with CSU may experience sleep disturbances, particularly due to itching. Biological rhythms (chronotypes) are categorized as morningness, intermediate, and eveningness types. This study evaluates the relationship between sleep quality, chronotype, and disease severity in CSU patients.
**Methods:** The study included 53 CSU patients and 50 healthy controls. A sociodemographic data form was completed, and the disease severity was determined utilizing the Urticaria Activity Score over 7 days (UAS7). The Hospital Anxiety and Depression Scale (HADS), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI) scales as well as the Morningness–Eveningness Scale (MEQ) were applied to the participants.
**Results:** The CSU group had a significantly higher body mass index (BMI) than that of the healthy control group. In terms of sleep and chronotype scales, compared to the control group, the CSU group had higher ISI scores as well as subscale scores on the PSQI subscales, with the exception of habitual sleep efficiency and total PSQI scores. There was no difference between MEQ scores. In the correlation analysis, the UAS7 and PSQI total scores were found to be correlated, whereas in the logistic regression analysis the estimated relative risk of BMI and PSQI total score for CSU was found to be 1.13 and 1.45, respectively.
**Conclusions:** When dealing with CSU patients, it is necessary to conduct a sleep quality assessment as part of a holistic evaluation.

**Keywords:** chronic spontaneous urticaria, chronotype, itch, sleep disruption, sleep quality

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## Introduction

Chronic spontaneous urticaria (CSU) is a dermatological disorder that lasts more than 6 weeks and is characterized by persistent or recurrent itchy lesions. It affects 0.5% to 1% of the general population (1). The average disease duration in CSU is reported to be 5 years, but this may be extended in the presence of concurrent angioedema or in combination with inducible urticaria or a positive autologous serum skin test (2–4). Women are approximately twice as likely as men to be affected. Infections (bacterial, viral, parasitic, and fungal), drugs, food additives, and foods are all blamed for its etiology, but in half of cases the cause cannot be determined. CSU is an autoimmune disease (1, 5).

Concurrently, CSU frequently coincides with mental health conditions such as depression, anxiety, and somatoform disorders, exacerbating the impact on an individual's overall wellbeing. Psychiatric disorders can significantly affect an individual's quality of life (6–8).

In recent years, there has been a significant resurgence in the acknowledgment and investigation of biological rhythms. These rhythms, also known as chronotypes, are typically classified into morningness, intermediate, and eveningness types (9). These three rhythms have distinct characteristics. Individuals with the morningness type get up early and go to bed early, and their sleeping hours vary less. Persons with the eveningness type have difficulty coping with stress and exhibit more physical symptoms, depression, and anxiety (9–11). Differences in chronotype preferences have previously been studied in many diseases but, as far as we know, no such study has been conducted in patients with CSU.

## Methods

### Study sample

The study design was a questionnaire-based and cross-sectional study including clinical assessment of urticaria severity. The study was commenced after ethics committee approval (decision no. 2011-KAEK-2_2020/271).

All participants signed written informed consent. Fifty-three patients with CSU and 50 healthy controls were included. All participants included in the study were 18 or older. Exclusion criteria included individuals with neurological diseases, cognitive impairment, malignancies, and psychiatric disorders, pregnant and breastfeeding women, and those taking antidepressant medications. In addition, shift workers were excluded from participation. Body mass index (BMI), drug use, disease duration, and dermatological examination of patients with CSU were recorded.

### Measurements

The Urticaria Activity Score over 7 Days (UAS7) is a patient-reported outcome tool to measure CSU activity. All parameters were evaluated using the following score scale of values: UAS7 score 28–42 = severe urticaria, 16–27 = moderate urticaria, 7–15 = mild urticaria, ≤ 6 = well-controlled urticaria (1).
The Italian version (12) of the Morningness–Eveningness Ques-

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tionnaire (MEQ) consists of 19 items. Participants are asked to indicate, among other things, their preferred time of waking and going to bed, as well as optimal times for mental and physical activity. When the scores of all items are summed, a total score ranging from 16 (extreme eveningness) to 86 (extreme morningness) is obtained. A total score above 58 defines morning types, and a score below 42 defines evening types (13).

The Pittsburgh Sleep Quality Index (PSQI) is a subjective assessment of sleep quality in the previous month. The scale consists of 19 questions. More points indicates more difficulty. A total score ≥ 5 indicates poor sleep quality (14).

The Insomnia Severity Index (ISI) assesses the perceived impact of sleep disturbance on an individual. The total score is between 0 and 28. Scores of 22–28 are considered severe insomnia, 15–21 clinical insomnia, 8–14 subclinical insomnia, and < 7 normal (15).

The Hospital Anxiety and Depression Scale (HADS) is a scale developed by Zigmond and Snaith (16). It is a 14-item test that includes anxiety and depression subscales. The scale makes it possible to quickly screen patients with a physical illness for depressive symptoms and anxiety.

### Statistical analysis

All statistical analyses were performed using the SPSS 20.0 software package. Continuous variables are expressed as mean ± standard deviation (*SD*), and the Student's t-test and Mann–Whitney U test were used to compare the means between the groups. Pearson and Spearman correlation were used for the correlation between UAS7 and other scale scores. Logistic regression was performed to evaluate the relative risk associated with CSU. A *p*-value < 0.05 was accepted as the significance level.

## Results

This study included 53 CSU patients and 50 controls. There was no statistically significant difference between the two groups in terms of age and sex, but the BMI of the CSU group was significantly higher than the control group ($p = 0.003$; Table 1). CSU had a mean disease duration of 29.76 ± 49.19 months and a UAS7 score of 24.26 ± 10.55. At the time of admission, 46 (86.7%) of the patients were taking medications; 22 (41.5%) were taking antihistamines, 22 (41.5%) were taking omalizumab, and two (3.7%) were taking both antihistamines and omalizumab. Angioedema was found in 40 (75.5%) of the CSU patients.

The PSQI total score, ISI, and HADS-Anxiety scores ($p < 0.001$, $p < 0.001$, and $p = 0.019$, respectively) were statistically significantly different. Sleep quality was lower, insomnia severity was greater, and anxiety level was higher in patients with CSU. There was no statistically significant difference in MEQ and HADS-Depression scores ($p > 0.05$). When the PSQI scale subgroups of the patient and control groups were examined, all showed a statistically significant difference (Table 2).

There was a statistically significant positive correlation between UAS7 and PSQI global score ($r = 0.290$ and $p = 0.035$). No significant difference was found between UAS7 scores and ISI, MEQ, and HADS scores (Table 3).

Logistic regression analysis was used to assess the risk factors

**Table 1** | **Demographic and clinical characteristics of the chronic spontaneous urticaria (CSU) and control group.**

| | Chronic urticaria *n* = 53 | Control *n* = 50 | *t/x²* | *p* |
|---|---|---|---|---|
| Age | 42.43 ± 11.92 | 41.36 ± 12.20 | 0.452* | 0.653 |
| Sex | | | 0.001† | 0.997 |
| Female | 35 | 33 | | |
| Male | 18 | 17 | | |
| Body mass index | 29.59 ± 5.60 | 26.61 ± 3.71 | 3.042* | **0.003** |
| Disease duration, month (mean ± *SD*) | 29.76 ± 49.19 | — | — | — |
| UAS (mean ± *SD*) | 24.26 ± 10.55 | — | — | — |
| Drug use for chronic urticaria, *n* (%) | 46 (86.7) | — | — | — |
| Antihistamines | 22 (41.5) | | | |
| Omalizumab | 22 (41.5) | | | |
| Combined | 2 (3.7) | | | |
| Angioedema, *n* (%) | 40 (75.5) | — | — | — |

UAS = Urticaria Activity Score, *SD* = standard deviation.
* = Student's *t*-test, † = chi-squared test.

**Table 2** | **Mean MEQ, PSQI, ISI, and HADS scores of participants.**

| | Chronic urticaria *n* = 53 | Control *n* = 50 | *t/z* | *p* |
|---|---|---|---|---|
| MEQ | 57.01 ± 6.14 | 57.60 ± 8.15 | −0.410* | 0.683 |
| PSQI Global score | 7.06 ± 3.95 | 3.48 ± 2.30 | **5.661*** | **< 0.001** |
| PSQI Subjective sleep quality | 1.37 ± 0.98 | 0.72 ± 0.60 | **3.792*** | **< 0.001** |
| PSQI Sleep latency | 1.22 ± 0.87 | 0.77 ± 1.52 | **−3.400†** | **0.001** |
| PSQI Sleep duration | 0.93 ± 0.93 | 0.53 ± 0.69 | **−2.041*** | **0.041** |
| PSQI Habitual sleep efficiency | 0.68 ± 1.08 | 0.24 ± 0.60 | −1.888† | 0.059 |
| PSQI Sleep disturbance | 1.35 ± 0.67 | 1.04 ± 0.82 | **−2.660†** | **0.008** |
| PSQI Use of sleep medication | 0.55 ± 1.11 | 0.04 ± 0.29 | **−3.018†** | **0.003** |
| PSQI Daytime dysfunction | 0.93 ± 1.13 | 0.35 ± 0.60 | **3.043*** | **< 0.001** |
| Mid-sleep time | 3.59 ± 1.27 | 3.55 ± 0.95 | −0.255† | 0.799 |
| Insomnia Severity Index | 9.48 ± 0.91 | 5.26 ± 0.59 | **4.186*** | **< 0.001** |
| HADS-Anxiety | 8.31 ± 4.27 | 6.27 ± 4.24 | **2.385*** | **0.019** |
| HADS-Depression | 6.78 ± 4.04 | 5.52 ± 3.97 | 1.565* | 0.121 |

MEQ = Morningness–Eveningness Questionnaire, PSQI = Pittsburgh Sleep Quality Index, ISI = Insomnia Severity Index, HADS = Hospital Anxiety and Depression Scale.
* = Student's *t*-test, † = Mann–Whitney *U* test.

for CSU (enter model). According to this analysis, the odds ratio (OR) of the PSQI global score for CSU was 1.45 (confidence interval [CI] 1.19–1.77) and the OR of BMI for CSU was 1.13 (CI 1.00–1.27). In summary, it has been determined that poor sleep quality and high BMI may be risk factors in the development of CSU (Table 4).

## Discussion

Except for the PSQI global score and habitual sleep efficiency, there was a significant difference between the subscale scores, ISI score, and HADS-Anxiety scores of the CSU group in this study. There was no statistically significant difference in the MEQ and HADS-Depression scores.

The skin is involved in many aspects of sleep activity, including thermoregulation and controlling sleep onset and waking up during the night. As a result, chronic dermatoses (which are typically itchy and/or painful) such as atopic dermatitis, psoriasis, CSU, prurigo nodularis, hidradenitis suppurativa, acne vulgaris, and lichen planus can significantly impair sleep quality (17).

Patients with CSU frequently experience sleep disturbances as a result of itching. Sleep-related complaints are reported by more than half of these patients (18, 19). Itching is linked to nocturnal awakening and difficulty falling asleep in CSU patients. In these patients, a deficiency in sleep has been associated with a decline in quality of life characterized by reduced energy levels (18). In a study that examined the relationship between CSU and sleep, the average PSQI score (4.5 points) was found to be significantly higher in CSU patients than in controls (4.0 points). There was a significant effect on sleep disturbance, sleep duration, daytime dysfunction, and sleep latency in the patient group, according to the findings. Furthermore, the severity of urticaria symptoms as measured by UAS-7 was found to be significantly related to poor sleep quality (i.e., PSQI scores) (20).

Grob et al. examined the effects of chronic dermatoses such as atopic dermatitis, chronic urticaria, and psoriasis on quality of life in 1,356 adult patients in their study. Patients with chronic urticaria and atopic dermatitis had more trouble sleeping than those with psoriasis (21). Mann et al. evaluated the relationship between insomnia and atopic dermatitis and chronic urticaria. The mean ISI score in patients with chronic urticaria was 6.8 prior to exacerbation and 14.9 during the attack, indicating an increase in insomnia during the attack. The findings of this pilot study suggest that itching may not be the only cause of insomnia in patients with chronic urticaria or atopic dermatitis, and more research is needed (22). In fact, this interpretation is remarkable, and when one looks at the literature it can be seen that sleep-related disorders in CSU patients have mostly been studied. However, the opposite situation—that is, how many people with sleep disorders develop CSU—is not well understood. Patients with sleep disorders were followed for 10 years in a cohort study conducted with a large population-based patient series on this subject. As a result, patients with sleep disorders were found to have a higher risk of developing CSU when compared to controls (23). In a survey of 208 patients, Yang et al. discovered that insomnia was a risk factor for CSU in patients that had experienced stress from major life events in the 6 months preceding the onset of symptoms (24). In our study, logistic regression analysis revealed that the estimated relative risk of a PSQI global score for CSU was 1.45. In other words, having a sleep disorder may be a factor that promotes the emergence of diseases such as CSU, and, when symptoms appear, insomnia due to itching increases, creating a vicious circle.

Circadian rhythms are important in a variety of biological functions. In terms of personality and behavioral characteristics, the types of morningness and eveningness differ greatly. There is a link between evening chronotype and maladaptive behaviors such as anxiety, attention deficit, and aggression, according to studies. Individuals with the eveningness type have more psychological and neurological issues than those with the morningness type (9). In a meta-analysis, it was discovered that people with an evening personality were more likely to experience severe mood symptoms (25).

There is very little information in the literature about the relationship between chronotype preferences and skin diseases. In 186 psoriasis patients, Henry et al. investigated the relationship between sleep quality, chronotype preference differences, and disease severity. The severity of the disease was found to be greater in patients that slept poorly. The mean MEQ score in the study was 51.4, and it was discovered that the chronotype prefer-

**Table 4** | **Logistic regression analysis enter model for chronic urticaria.**

| | B | *SE* | Wald | Sig. | Exp(B) | 95% CI |
|---|---|---|---|---|---|---|
| 1. Age | 0.004 | 0.023 | 0.033 | 0.857 | 1.004 | 0.96–1.05 |
| 2. Sex | 0.143 | 0.518 | 0.076 | 0.783 | 1.154 | 0.41–3.18 |
| 3. PSQI-G | **0.376** | **0.101** | **13.796** | **< 0.001** | **1.456** | 1.19–1.77 |

PSQI-G = Pittsburgh Sleep Quality Index–global score, B = regression coefficient, *SE* = standard error of the regression coefficient, Wald = Wald statistic, Sig. = statistical significance, Exp (B) = exponentiated regression coefficient, CI = confidence interval.

**Table 3** | **Pearson and Spearman correlation coefficients.**

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| 1. UAS | *r* | 1 | | | | | | |
| | *p* | | | | | | | |
| 2. MEQ | *r* | −0.087[a] | 1 | | | | | |
| | *p* | 0.536 | | | | | | |
| 3. PSQI-G | *r* | **0.290[a]** | −0.032[a] | 1 | | | | |
| | *p* | **0.035** | 0.837 | | | | | |
| 4. ISI | *r* | 0.272[a] | −0.029[a] | **0.695[a]** | 1 | | | |
| | *p* | 0.051 | 0.839 | **< 0.001** | | | | |
| 5. HADS-A | *r* | 0.045[a] | −0.263[a] | **0.363[a]** | **0.489[a]** | 1 | | |
| | *p* | 0.754 | 0.063 | **0.009** | **< 0.001** | | | |
| 6. HADS-D | *r* | 0.094[a] | −0.125[a] | **0.467[a]** | **0.441[a]** | 0.674[a] | 1 | |
| | *p* | 0.510 | 0.381 | **0.001** | **0.001** | < 0.001 | | |
| 7. MST | *r* | −0.059[b] | **−0.302[b]** | −0.188[b] | −0.199[b] | −0.200[b] | −0.048[b] | 1 |
| | *p* | 0.673 | **0.028** | 0.216 | 0.157 | 0.159 | 0.737 | |

UAS = Urticaria Activity Score, MEQ = Morningness–Eveningness Questionnaire, PSQI-G = Pittsburgh Sleep Quality Index–global score, ISI = Insomnia Severity Index, HADS-A = Hospital Anxiety and Depression Scale–anxiety subscale, HADS-D = Hospital Anxiety and Depression Scale–depression subscale, MST = mid-sleep time.

[a] = Pearson correlation coefficient used, [b] = Spearman correlation coefficient used.

ence of more than half (62.9%) of the patients was intermediate (26). Similarly, the mean MEQ score in the CSU group in this study was 57.01, and the chronotype preference of most patients was intermediate. There was no significant difference between the two groups in our study, but according to the literature roughly 60% to 70% of the population falls into the intermediate chronotype group and has a moderate sleep pattern between the two extreme types (27). The patient group mirrored society in this regard. Bilgili et al. investigated the role of chronotype differences in the circadian pattern of chronic pruritus. Whereas eveningness patients reported more severe itching symptoms earlier in the day, morningness patients reported more severe itching symptoms later in the day. The authors hypothesized that there was a link between the severity of pruritus and chronobiological and psychosomatic factors (28). There are many studies examining the relationship of chronobiology with rheumatoid arthritis, the exact cause of which is unknown, but it shares autoimmune factors similar to CSU in its etiology. Habers et al. studied the relationship between chronotype and disease activity in rheumatoid arthritis patients. However, they discovered no link between chronotype and disease activity (29). To the best of our knowledge, there are no studies in the literature that examine chronotype differences in patients with CSU.

Numerous studies in the literature show that patients with CSU have a low quality of life. Depression and anxiety are the most common psychiatric disorders among these patients, both of which have a negative impact on their quality of life (6, 30). Because there are insufficient data on this subject, it is unclear whether the presence of depression and anxiety prior to the onset of CSU worsens symptoms. Choi et al. used HADS to assess anxiety and depression levels in 79 chronic urticaria patients. Depression was found to be related to sleep disorders, anxiety to the severity of pruritus and urticaria, and stress to the severity of sleep disturbance, itching, and urticaria in chronic urticaria patients (31). Rafique et al. recently examined depression and anxiety symptoms in 146 patients with CSU. Depression and anxiety were present in 39 of the participants (26.7%), and they were more common in those with a family history of mental disorders (32). Another study found that nearly half of CSU patients (47.3%) had severe anxiety symptoms, and 29.1% had moderate anxiety symptoms (33). Similarly, in our study, HADS-Anxiety scores were found to be significantly higher in the CSU group. In terms of HADS-Depression scores, there was no statistically significant difference between the two groups, but the CSU group had a higher score. We believe that studies with larger patient series may show a difference.

There are several limitations of this study. It is a cross-sectional study, and the scales are based on the participants' own statements. Although self-report forms are functional from time to time, they may fail to evaluate the overall situation because they reflect the immediate situation of the individual.

## Conclusions

The disease itself should not be the only focus in the management of CSU patients. Because itching or disease activation may not be the only cause of sleep-related problems in these patients, it is critical to consider the presence of underlying sleep disorders and psychiatric conditions. In this highly chronic disease that has a negative impact on patients' quality of life, taking a holistic approach to patients and identifying the underlying issues are just as important as treating the dermatological disease.

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