

Association of sleep quality and mucosal healing in patients with inflammatory bowel disease in clinical remission

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Abstract

Background The interaction between sleep and the immune system has been increasingly studied over the last decades. The aim of this study was to investigate the association between sleep quality and mucosal healing in patients with inflammatory bowel disease (IBD) currently in clinical remission.

Methods Ninety patients with IBD in clinical remission were studied: 54 (60%) with Crohn's disease and 36 (40%) with ulcerative colitis. All completed the Pittsburgh Sleep Quality Index, and mucosal healing was estimated with ileocolonoscopy. A subgroup analysis was also performed in order to investigate these associations in Crohn's disease and ulcerative colitis separately.

Results Of the 90 patients, 45.56% had poor sleep quality. Patients without mucosal healing expressed higher absolute values of the Pittsburgh Sleep Quality Index ($P < 0.001$), while absence of mucosal healing and poor sleep quality were statistically associated ($P < 0.05$). Subgroup analysis showed that the same pattern was present in patients with Crohn's disease: patients without mucosal healing expressed higher absolute values of the Pittsburgh Sleep Quality Index ($P < 0.001$) and the absence of mucosal healing was statistically associated with poor sleep quality ($P < 0.05$). However, these associations were not observed in the subgroup of patients with ulcerative colitis ($P > 0.05$).

Conclusion In patients with IBD in clinical remission, absence of mucosal healing seems to be associated with poor sleep quality, especially in patients with Crohn's disease.

Keywords Inflammatory bowel disease, sleep quality, mucosal healing, Pittsburgh Sleep Quality Index

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Introduction

The interaction between sleep and the immune system has been increasingly studied over the last decades. It has been demonstrated that several inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α , produced in many chronic inflammatory diseases such as inflammatory bowel disease (IBD) and rheumatoid arthritis, can affect the sleep-wake cycle and induce sleep disorders [1-3]. Two recent studies have shown that anti-TNF treatment in patients with rheumatoid arthritis and ankylosing spondylitis improves sleep quality [4,5].

Conversely, there are studies indicating that sleep deprivation can induce inflammatory cytokine production [6-9], and may also influence the cellular immune components, such as natural killer cells [10]. In one study, the authors demonstrated that acute and chronic sleep deprivation can exacerbate colonic inflammation in mouse models of IBD [11].

Interest in the interaction of sleep disturbances and IBD has increased even more since the establishment of the "treat-to-target" approach, which incorporates patient-reported outcomes (PROs) in our therapeutic targets [12]. Most authors include fatigue in such PROs and many include sleep quality, which seems to be an important factor associated with quality of life and with the aforementioned development of fatigue [12,13]. Recent studies have shown that IBD patients suffer more from sleep disorders than do normal controls and that there is a strong association between sleep disorders and active IBD [14,15]. Moreover, Ananthakrishnan *et al*, in a large study that included 3173 participants, found that patients with Crohn's disease (CD) who reported sleep disturbances were at risk of developing clinically active disease in the following 6 months [16]. However, the same effect was not demonstrated for patients with ulcerative colitis (UC) [16]. Similar results, but accounting for both CD and UC were also found in a study involving 177 Japanese patients, which demonstrated an increased risk for IBD flare within one year in patients with sleep disorders [17].

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Conflict of Interest: None

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Taking into account that there is only one study, involving only 18 patients, that refers to the association of sleep quality with mucosal disease activity in IBD patients in clinical remission [15], we performed a larger study that aimed to investigate the association of sleep quality and mucosal healing in patients with IBD in clinical remission.

Patients and methods

Patients and definitions

This was a cross-sectional single-center study. Ninety patients with IBD were included in the study, 54 (60%) with CD and 36 (40%) with UC. All patients were examined in our outpatient clinic during the period from January 2015 to January 2016 and were found to be in clinical remission. "Clinical remission" in the case of CD was defined as a CD Activity Index (CDAI) <150, while in the case of UC, "clinical remission" was defined as a partial Mayo Score (pMayo score) ≤2. To estimate the patients' sleep quality the Pittsburgh Sleep Quality Index (PSQI), an easy-to-use and validated instrument, was used with permission [18]. Consisting of 19 items, the PSQI measures different aspects of sleep, offering seven component scores and one composite score. The component scores consist of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each item is graded on a scale of 0-3. The global PSQI score is then calculated by totaling the seven component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality [18].

Since the population under study were not native English speakers, we used the validated Greek-language version of PSQI (GR-PSQI) [19]. All patients completed the questionnaire and the index was calculated using the PSQI Scoring Database. A score ≤5 indicated "good sleep quality", while a score >5 indicated "poor sleep quality", according to the authors' instructions [18].

Mucosal healing was estimated with ileocolonoscopy on the same day that the PSQI calculation was performed. All 90 patients underwent ileocolonoscopy and mucosal healing was defined as an endoscopic Mayo score ≤1 in the case of UC, an absence of ulcers in the case of CD, and a Rutgeert's score <2 in the case of CD postoperatively. Data regarding age, sex, treatment for IBD, duration of the disease, history of surgery related to IBD, perianal disease in CD and medically diagnosed depression were also collected.

Methodology

A separate analysis was performed for IBD patients in total, followed by subgroup analysis for CD and UC patients separately. To avoid bias, the ileocolonoscopy was performed by a different gastroenterologist than the one who calculated the CDAI, pMayo score and PSQI.

Statistical analysis

Statistical analysis of the acquired data was performed with Stata 9.0 software (StataCorp, College Station, TX). All comparisons utilised a two-sided significance level of 0.05. A univariate ANOVA regression analysis using the PSQI absolute value as dependent value was performed for the IBD group and also for the two subgroups (CD and UC). Variables that reached statistical significance on univariate analysis at $P < 0.05$ were included in the multivariate model. A value of $P < 0.05$ was used as a threshold for statistical significance in the multivariate model. The chi-square test and Fisher's exact test were used appropriately in order to estimate the association between mucosal healing and poor sleep quality (expressed as $PSQI > 5$) in the main group and the two subgroups. Sample size was calculated using G-power so that a between-group difference in patients with and without mucosal healing would permit a one-tailed type I error rate of $\alpha = 0.05$ with a power of 80%. This analysis indicated that a sample size of at least 39 patients per group was necessary.

Ethical statement

The study protocol conformed to the ethical principles for medical research including human subjects described in the Declaration of Helsinki and was approved by the hospital's ethics committee. All patients participating in the study signed an informed consent form.

Results

Patient characteristics

The descriptive characteristics are presented in Table 1.

Factors associated with higher PSQI values and poor sleep quality in IBD patients

According to the results of univariate ANOVA regression analysis with the PSQI absolute value as dependent value (Table 2), a positive association with higher absolute PSQI values was observed for female sex ($P = 0.024$), and for medically diagnosed depression ($P = 0.044$). Patients with an absence of mucosal healing also expressed higher absolute values of PSQI ($P < 0.001$). Further analysis of this group with multivariate ANOVA regression analysis (Table 2) revealed that only female sex ($P = 0.011$) and absence of mucosal healing ($P < 0.001$) were associated with higher PSQI values. No statistically significant association was observed for the rest of the variables (age, duration of disease, treatment, and surgery). To explore the association between the absence of mucosal healing and poor sleep quality, defined by values of $PSQI > 5$, the chi-square test was performed, resulting in a statistically significant association ($P < 0.05$) between the two variables. It seems that in IBD patients in clinical remission, absence of mucosal healing is associated with poor sleep quality.

Factors associated with higher PSQI values and poor sleep quality in patients with CD

According to the results of univariate ANOVA regression analysis with the PSQI absolute value as dependent value in CD patients (Table 3), a positive association was observed only with absence of mucosal healing ($P<0.001$), thus showing that patients with CD and absence of mucosal healing, as estimated

by ileocolonoscopy, had higher absolute PSQI values compared to patients with mucosal healing (Fig. 1). Chi-square test analysis also revealed that, in patients with CD, absence of mucosal healing and poor sleep quality, defined as $PSQI>5$, were also statistically significantly associated ($P<0.05$). It seems that in patients with CD, absence of mucosal healing in patients with clinical remission was associated with poor sleep quality.

Table 1 Descriptive characteristics of IBD, UC and CD patients

Patient characteristics	IBD (n=90)	UC (n=36)	CD (n=54)
Age	40.5±14.7	45.4±15.1	37.3±13.6
Sex (females)	42 (46.67%)	14 (38.89%)	28 (51.85%)
Duration of disease (years)	7.6±7.4	10.2±9.3	6±5.4
PSQI (>5)	41 (45.56%)	14 (38.89%)	27 (50%)
PSQI absolute value	5.7±3.4	5.6±3.8	5.8±3.2
Treatment			
None	2 (2.22%)	1 (2.7%)	1 (1.8%)
5-ASA	36 (40%)	23 (63.88%)	13 (24.07%)
Azathioprine	14 (15.56%)	3 (8.33%)	11 (20.37%)
Infliximab	26 (28.89%)	8 (22.2%)	18 (33.33%)
Adalimumab	11 (12.22%)		11 (20.37%)
Azathioprine+5-ASA	1 (1.11%)	1 (2.7%)	
Absence of mucosal healing	39 (43.33%)	13 (36.11%)	26 (48.15%)
Depression under treatment (yes)	8 (8.89%)	2 (5.56%)	6 (11.11%)
Surgery (yes)	11 (12.22%)	0 (0%)	11 (20.37%)

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; PSQI, Pittsburgh sleep quality index; 5-ASA, 5-aminosalicylates

Table 2 Univariate and multivariate ANOVA regression analysis using PSQI absolute value as dependent variable (IBD patients)

PSQI absolute (univariate)	Coefficient	SE	P-value	95%CI
Sex (female)	1.64	0.71	0.024	0.21-3.06
Age	0.04	0.02	0.06	-0.002-0.09
Duration of disease	-0.003	0.05	0.94	-0.1-0.1
Treatment				
(5-ASA)	5.9	0.59	Reference	4.79-7.15
Azathioprine	0.45	1.12	0.685	-1.77-2.68
Infliximab	-0.74	0.91	0.42	-2.56-1.07
Adalimumab	-0.33	1.22	0.785	-2.77-2.1
Azathioprine+5-ASA	1.02	3.6	0.776	-6.14-8.19
Absence of mucosal healing	2.99	0.67	<0.001	1.6-4.3
Depression under treatment (yes)	2.58	1.26	0.044	0.07-5.10
Surgery (yes)	0.78	1.12	0.48	-1.44-3.01
PSQI absolute (urivariate)				
Absence of mucosal healing	3	0.65	<0.001	1.71-4.29
Sex (female)	1.66	0.64	0.011	0.38-2.95

SE, standard error; CI, confidence interval; PSQI, Pittsburgh sleep quality index; IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylates

Factors associated with higher PSQI values and poor sleep quality in patients with UC

From univariate ANOVA regression analysis with the PSQI absolute value as dependent value in UC patients (Table 4), a positive association was observed only for female sex ($P=0.008$), but no association was found regarding mucosal healing (Fig. 2). Fisher's exact test was also performed in this group in order to determine whether there was any association between poor sleep quality ($PSQI>5$) and mucosal healing, but no significant results were revealed ($P>0.05$). In UC it seems that only female sex was associated with higher PSQI values, and that mucosal healing in patients in clinical remission was not associated with sleep quality.

Discussion

The relationship between sleep quality and the immune system is complex and has been studied extensively in the past decades. It

has previously been demonstrated that sleep deprivation may cause alterations in immune function and may promote the production of inflammatory cytokines, and that chronic inflammatory disorders are associated with disturbances of the sleep-wake cycle [6,7,19-21]. Sleep restriction and sleep apnea can result in tissue hypoxia, oxidative stress, sympathetic activation, and systemic inflammation, leading to activation of inflammatory cytokines such as TNF, IL-1, and IL-6 [22]. Interestingly, these cytokines (IL-1, IL-6, and TNF- α) are also implicated in the pathogenesis of IBD [1-3]. There are also data suggesting that circadian clock genes are involved in the regulation of the gastrointestinal physiology, while it has been shown in experimental models that disruption of the circadian clock may increase intestinal permeability, thus enabling the translocation of bacterial proinflammatory products (endotoxins etc.) and activating an inflammatory cascade [23]. Melatonin, a neurohormone produced by the pineal gland and by enterochromaffin cells in the gastrointestinal tract, has also gained interest in studies of the association between sleep disturbances and IBD. Melatonin promotes sleep by reducing sleep latency,

Table 3 Univariate ANOVA regression analysis using PSQI absolute values as dependent variable (CD)

PSQI absolute	Coefficient	SE	P-value	95%CI
Sex (female)	0.53	0.88	0.55	-1.24-2.3
Age	0.05	0.03	0.11	-0.01-0.11
Duration of disease	-0.04	0.08	0.57	-0.21-0.12
Treatment				
(5-ASA)	6.23	0.9	Reference	4.41-8.04
Azathioprine	0.86	1.33	0.523	-1.82-3.54
Infliximab	-1.28	1.18	0.284	-3.6-1.09
Adalimumab	-0.59	1.33	0.658	-3.27-2.08
Absence of mucosal healing	3.62	0.73	<0.001	2.15-5.09
Depression under treatment (yes)	2.04	1.38	0.14	-0.73-4.82
Surgery (yes)	0.75	1.09	0.49	-1.44-2.96
Perianal disease	0.91	1.31	0.48	-1.77-3.55

SE, standard error; CI, confidence interval; PSQI, Pittsburgh sleep quality index; CD, Crohn's disease; 5-ASA, 5-aminosalicylates

Table 4 Univariate ANOVA regression analysis using PSQI absolute value as dependent variable (UC)

PSQI absolute	Coefficient	SE	P-value	95%CI
Sex (female)	3.39	1.2	0.008	0.95-5.83
Age	0.05	0.04	0.23	-0.03-0.14
Duration of disease	0.029	0.07	0.7	-0.12-0.18
Treatment				
(5-ASA)	5.82	0.83	Reference	4.11-7.53
Azathioprine	-1.82	2.46	0.465	-6.85-3.2
Infliximab	0.04	1.64	0.977	-3.31-3.41
Azathioprine+5-ASA	1.17	4.1	0.777	-7.19-9.54
Absence of mucosal healing	2	1.31	0.13	-0.65-4.67
Depression under treatment (yes)	4.08	2.75	0.14	-1.5-9.6
Surgery (yes)	-	-	-	-

SE, standard error; CI, confidence interval; PSQI, Pittsburgh sleep quality index; UC, ulcerative colitis; 5-ASA, 5-aminosalicylates

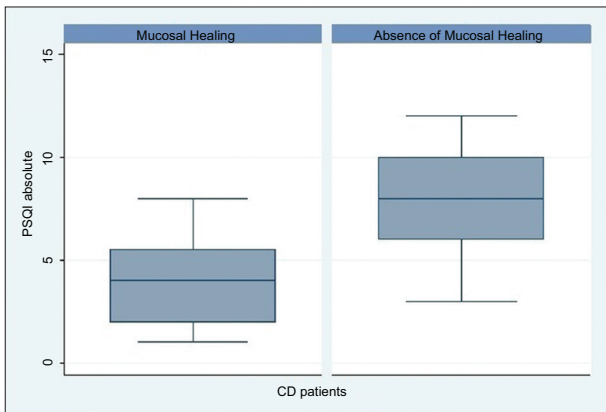


Figure 1 Median PSQI absolute values in CD patients with and without mucosal healing

PSQI, Pittsburgh sleep quality index; CD, Crohn's disease

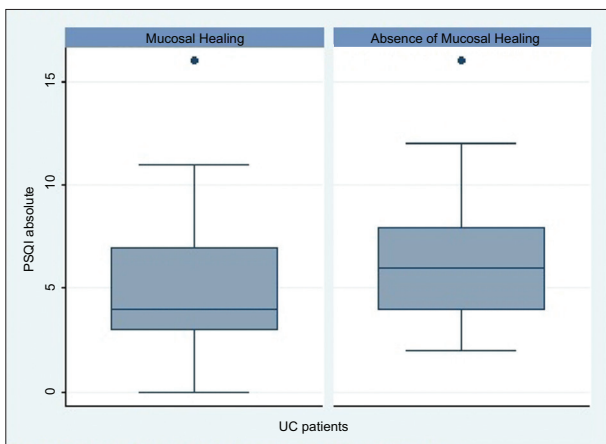


Figure 2 Median PSQI absolute values in UC patients with and without mucosal healing

PSQI, Pittsburgh sleep quality index; UC, ulcerative colitis

decreasing wake time, and increasing overall sleep quality. In addition, it seems to exert some immunomodulatory effect through the modulation of antioxidant and anti-inflammatory pathways and by playing a protective role against mucosal ulceration [24].

On the other hand, as mentioned above, it has also been demonstrated that inflammatory cytokines produced by chronic inflammatory diseases may in turn influence the sleep-wake cycle and induce sleep disorders [1-3]. Moreover, patients with IBD experience sleep disruption due to nocturnal diarrheas, abdominal pain, extraintestinal manifestations, stress and depression, which in turn may lead to a vicious cycle of poor sleep quality and increased inflammatory response [24]. In fact, nocturnal diarrheas and abdominal pain have been implicated in affecting the sleep quality of IBD patients [25].

Regarding clinical data, Ranjbaran *et al* demonstrated that IBD patients, even with clinically inactive disease, had significant sleep disturbances in comparison to healthy subjects [14]. In the current study it was shown that 45.56% of patients in clinical remission had poor sleep quality expressed as a PSQI score >5. This percentage is in accordance with the findings of a large study by Graff *et al*, who studied 318 IBD patients, and demonstrated that 49% of those with inactive disease had an abnormal PSQI score [26].

In 2013, Ali *et al* demonstrated that sleep quality was associated with disease activity, since the authors found that all patients with clinically active disease had sleep disturbances [15]. This fact of course could be attributed to some extent to other coexisting factors, such as pain, nocturnal diarrhea, presence of extraintestinal manifestations, stress associated with the disease activity, or even specific treatments for IBD, such as corticosteroids. Interestingly, they also demonstrated that an abnormal PSQI had a positive predictive value of 83% for histological inflammatory activity, even among patients with clinically inactive disease. However, it must be noted that in this study the number of patients with inactive disease was relatively small (18 patients) [15].

In the current study, 90 patients with IBD in clinical remission were enrolled and it was evident that abnormal PSQI was associated with the absence of mucosal healing as estimated with ileocolonoscopy. It was also demonstrated that patients with absence of mucosal healing had higher absolute PSQI values than patients with mucosal healing. Bearing in mind that the population under investigation was in clinical remission, this association cannot be attributed to IBD symptoms and was most probably associated with the effect of inflammatory cytokines, as discussed above. However, it cannot be safely concluded from this observation whether sleep disturbance precedes the emergence of mucosal lesions, or whether subclinical disease activity in terms of mucosal lesions is the cause of sleep disturbance.

Another interesting observation revealed by this study is that, in subgroup analysis for CD and UC separately, a statistically significant association between sleep quality and mucosal healing status was demonstrated for patients with CD in clinical remission and also that patients with absence of mucosal healing had higher absolute PSQI values than patients with mucosal healing. On the other hand, in patients with UC there was no association between sleep quality and mucosal healing status. A similar pattern was demonstrated by the large study of Ananthakrishnan *et al*, with 3173 IBD patients, in which it was shown that patients with CD who reported sleep disturbances were at risk of clinically active disease within 6 months, but this association was not demonstrated for patients with UC [16]. The reason for this divergence between CD and UC cannot be adequately explained, but it must be kept in mind that although these two diseases share common characteristics and gene loci, they have different expression and follow different pathogenetic pathways. Furthermore, the fact that CD is a disease causing transmural inflammation, in contrast to UC, which is confined to the mucosa, may be associated with a different burden of inflammatory cytokines. Finally, it has been previously established that some environmental factors, such as smoking and a history of appendectomy, have different effects in CD and UC. Sleep quality may be another factor with different effects on these two diseases.

Regarding the limitations of this study, one major limitation is the fact that there was no estimation of depression with the use of any of the available questionnaires. Use of such questionnaires might lead to more unbiased results, since depression is a factor that is known to influence sleep quality and is also relatively common among IBD patients [27,28]. Nevertheless, information regarding medically diagnosed depression and depression treatment was ascertained during the acquisition of each patient's history and was included in

Summary Box

What is already known:

- Inflammatory bowel disease (IBD) patients suffer more from sleep disorders than do normal controls
- Acute and chronic sleep deprivation can exacerbate colonic inflammation in IBD mouse models
- Inflammatory cytokines can affect the sleep-wake cycle and induce sleep disorders

What the new findings are:

- Patients with Crohn's disease showed a statistically significant association between sleep quality and mucosal healing status
- In patients with ulcerative colitis there was no association between sleep quality and mucosal healing status

the multivariate analysis; however, no statistically significant association was found. A second limitation is the fact that no data were collected regarding extraintestinal manifestations that could also influence sleep quality, such as arthralgia or arthritis.

The results of our study have several implications, since it demonstrated that almost half of IBD patients in clinical remission have poor sleep quality, and also that in patients with CD, this poor sleep quality may be associated with subclinical mucosal disease activity. We believe that sleep disturbances may express an extraintestinal manifestation and that they should be addressed in our patients in everyday clinical practice. Moreover, in the case of CD, the presence of poor sleep quality estimated with the use of PSQI, which is an easy-to-use score, can act as an indirect indicator of subclinical disease activity. There is an emerging need for further research regarding the potentials of medical interventions targeting sleep disturbances in patients with IBD and their effect on the disease course.

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