Quality of Sleep in Patients with Celiac Disease
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Quality of Sleep in Patients with Celiac Disease

Fabiana Zingone, Monica Siniscalchi, Pietro Capone, Raffaella Tortora, Paolo Andreozzi, Elisa Capone*, Carolina Ciacci

Department of Clinical and Experimental Medicine Federico II University of Naples, Italy

*Second University of Naples, Italy

Address for correspondence:

Dr Carolina Ciacci, MD
Gastroenterology
Dep. Clinical and Experimental Medicine
Via Sergio Pansini, 5 80131 Naples ITALY
tel/fax: +39081746 4270 e-mail: ciacci@unina.it

Key words: sleep quality, quality of life, celiac disease

Short title: sleep and celiac disease
ABSTRACT

Background: Celiac disease (CD) is a chronic disease with a various clinical presentation, including anxiety and depression.

Aim: This study investigated the quality of sleep in CD.

Methods: The participants were celiacs at diagnosis (C-N); celiacs on gluten free diet at follow-up (C-T); and healthy volunteers (HV). Participants completed the Pittsburgh Sleep Quality Index (PSQI), SF36, Zung and Fatigue scales, and State-Trait Anxiety Inventory (STAI).

Results: The PSQI score was higher in C-N and C-T than in HV ($p<0.001$). A gluten-free diet (GFD) did not improve the PSQI scores ($p=0.245$) in CD. The other test scores were similar between celiacs at diagnosis and those on a GFD, while significant differences were found between celiacs and volunteers. PSQI score was inversely associated with the quality of the physical ($r=-0.327$, $p=0.002$) and mental ($r=-0.455$, $p<0.001$) components scores.

The sleep quality scores were related to depression ($r=0.633$, $p<0.001$), fatigue ($r=0.377$, $p<0.001$), state anxiety ($r=0.484$, $p<0.001$), and trait anxiety ($r=0.467$, $p<0.001$).

Conclusions: Sleep disorders are common in CD also during treatment with GFD. Sleep disorders are related to depression, anxiety and fatigue, and inversely related to quality of life scale scores.
INTRODUCTION

In the general population, increased stress, anxiety, depression and worry are associated with poor subjective sleep quality (1). In addition, common medical problems are often associated with abnormalities of sleep. In fact, patients with chronic medical disorders often have fewer hours of sleep and less restorative sleep, as compared to healthy individuals, and this poor sleep may worsen the subjective symptoms of the disorder (2). Among gastrointestinal diseases, gastroesophageal reflux is a major cause of disrupted sleep due to awakenings from heartburn, dyspepsia, coughing, or choking (3). Other gastrointestinal diseases have not been studied.

Celiac disease is a chronic disease presenting with a broad spectrum of symptoms and signs. Anxiety, depression, and other mood disorders are associated with celiac disease (4-7). More recently, restless legs syndrome has been shown to be frequent in celiac disease (8). Most of the above-mentioned conditions may affect sleep. As the quality of sleep in celiac disease has not been investigated systematically, this study investigated the quality of sleep in a cohort of adult celiac patients.

MATERIALS AND METHODS

The study population consisted of adult celiacs consecutively recruited from September 2009 to March 2010 from the Celiac Disease Centre of Federico II University (Naples, Italy) and sex- and age-matched volunteers recruited from the hospital staff and friends of CD patients. The study was approved by the Ethical Committee of the Federico II University of Naples (Diagnosis and Follow-up of Celiac Disease n10/2003-2013).
The celiacs were divided into two groups: celiac patients at diagnosis on gluten-containing diet (celiac-new, C-N) and celiac patients at follow-up on gluten free diet, since at least one year and with negative anti-transglutaminase IgA antibody (celiac-treated, C-T).

Questionnaires were administered in the morning of the annual visit which is required after CD diagnosis for coverage the costs of gluten free food by the Italian National Health System. None of patients refused to answer to this questionnaire. For all celiac patients, the diagnosis was based on the presence of anti-transglutaminase IgA and anti-endomysium antibodies and an intestinal biopsy compatible with gluten-related damage. The control group (healthy volunteer, HV) consisted of individuals who were tested and found negative for serum markers of celiac disease.

Data were collected on age, gender, marital status, education and laboratory nutritional indices. The inclusion criteria of the study cohort were written informed consent, age 19 to 60 years, absence of major psychiatric disease, absence of cancer, and no pregnancy or children below 3 years old that may affect the quality and modality of sleep.

**Pittsburgh Sleep Quality Index**

All participants completed the Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep quality. The PSQI was developed to measure sleep quality during the previous month and to discriminate between good and poor sleepers. Sleep quality is a complex phenomenon that involves several dimensions, each of which is covered by the PSQI. The domains covered include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, the use of sleep medications, and daytime dysfunction.
The PSQI consists of 19 self-rated questions and five questions rated by a bed partner or roommate (only the self-rated items are used in scoring the scale). The self-administered portion consists of 15 multiple-choice items that inquire about the frequency of sleep disturbances and subjective sleep quality, and four write-in items that inquire about typical bedtime, wake-up time, sleep latency and sleep duration. The PSQI generates seven scores that correspond to the domains listed previously. Each component score ranges from 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range 0–21). A PSQI global score >5 is suggestive of significant sleep disturbance (9,10).

To evaluate possible factors contributing to sleep quality, the SF-36 questionnaire, Zung Self-rating Depression Scale, State-Trait Anxiety Inventory and a Fatigue visual analogue scale (VAS), were administered.

**SF-36 questionnaire**

The SF-36 survey consists of a 36-item questionnaire that includes eight components: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional health, and mental health. These eight domains form two broader health dimension scales: the physical (PCS) and mental (MCS) component scales. The SF-36 subscales and composite scores are presented as means and standard deviations and range from 0 to 100, with higher scores indicating better health and well-being. The PCS and MCS composite means and standard deviations are 50±10 for the U.S. general population. PCS and MCS factors have been found to account for 80~85% of the reliable variance in the eight SF-36 scales in patients, as well as
in general populations (11-13). Poor (low) scores on the PCS indicate limitations in physical/role functions and general health, and bodily pain, while better (higher) scores suggest no physical limitations, disabilities, or decrements in well-being. Similarly, low scores on the MCS suggest frequent limitations in psychosocial health, emotional problems, and reduced vitality (a fatigue construct), while high scores indicate frequent positive affect and vitality, the absence of psychological distress, and reduced or no limitations in daily social and role activities.

**ZUNG Self-rating Depression Scale**

The Zung Self-rating Depression Scale is a 20-item self-report questionnaire that is widely used as a screening tool, covering affective, psychological, and somatic symptoms associated with depression (14,15). In this study, depressive symptoms were assessed by a modified version of the Zung Self-rating Depression Scale (M-SDS), which contains 17/20 items belonging to the original version of the Zung scale (5,7,16). Three items for gastroenterological symptoms of depression (decreased appetite, weight loss, and constipation) were eliminated to avoid the possible bias due to CD. The cut-off score of the M-SDS scale, for pathological depression is 44.

**Fatigue visual analogue scale**

This consisted of a single question: ‘How did you feel during last week?’ The patients were asked to mark a visual analogue scale (VAS) consisting of a 10-cm line with ‘I never feel tired’ at the left end and ‘I always feel tired’ at the opposite end. Therefore, the possible score ranges from 0 to 10 (5).
State-Trait Anxiety Inventory

Anxiety was assessed using the State-Trait Anxiety Inventory (STAI), which consists of two axes (y1 for state anxiety and y2 for trait anxiety), both consisting of 20 multiple-choice items; the STAI can distinguish between existing anxiety and a predisposition to anxious reactions as a personality characteristic, as previously described (17). This theory is based on the conceptual distinction between anxiety as a transitory state and anxiety as a relatively stable personality trait. State anxiety is conceptualised as an emotive state characterised by subjective feelings perceived on a conscious level, such as apprehension and tension, which varies with time; anxiety as a trait refers to individuals with an on-going disposition towards anxiety (18). The subjects evaluated were grouped as high- and low-anxious and a value of 40 was used to distinguish between the two groups, according to Spielberg et al. (19) and Weinstein (20).

STATISTICAL ANALYSIS

Chi-square analysis and ANOVA were used for analyses on categorical and continuous data, respectively. Continuous data were reported as means ± standard deviation (SD). Categorical data were given as counts and percentages. The Spearman correlation coefficient was used to test for correlations between sleep quality and quality of life scores, depression scale, fatigue severity, STAI scores, and age. The Statistical Package for Social Sciences (SPSS) 13.0 was used to analyze the data. A p value ≤ 0.05 was considered significant.
RESULTS

The study cohort consisted of three groups of 30 subjects each (10 males, 20 females). The age at time of testing, education and marital status were similar among the three groups (Table 1). The patients in C-T had been on a gluten-free diet for 6±5.9 years.

Nutritional indices were significantly different in C-N and C-T (blood hemoglobin: 11.67±0.87 g/dL and 12.3±0.52 g/dL respectively, \( p = 0.002 \); plasma cholesterol: 165.6±13.47 mg/dL and 191.46±21.73 mg/dL respectively, \( p < 0.001 \); serum albumin: 3.67±0.88 mg/dL and 4.09±0.37 mg/dL respectively, \( p < 0.001 \); body mass index: 21.6±2.55 Kg/m\(^2\) and 24.8±3.43 Kg/m\(^2\) respectively, \( p = 0.007 \)).

PSQI results

A progressive decrease of the score indicating pathological sleep, was found among the three groups (\( p < 0.001 \)). The comparison between the two celiac groups indicated that the PSQI score, did not differ between C-N and C-T (\( p > 0.2 \)) (Table 2).

The analysis of the single domains of the PSQI (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction) indicated a significant difference between celiac patients (both C-N and C-T) and volunteers for each domain (\( p < 0.05 \)), except for sleep duration, which was similar in the three groups (\( p = 0.166 \)).

SF36 results

The comparison of each single domain of the SF36 and the PCS and MCS values did not show differences between celiacs at diagnosis and celiac on a gluten-free diet. The quality...
of life of CD patients, (C-N and C-T) was significantly lower than that of the volunteers for each domain (Figure 1).

**Zung, fatigue, and anxiety scale results**

Celiac patients showed a significant difference in the modified Zung scale scores, fatigue VAS scores, and STAI y1 and y2 scale scores, as compared to volunteers. The results did not significantly differ between untreated celiacs and celiacs on gluten free diet (Table 3).

Only two persons from C-N and two from C-T had a modified Zung score above the threshold for major depression. Findings were similar after the exclusion of these patients (C-N 5.92±3.52; C-T 4.82±2.14; HV 2.96±2.86; p= 0.001).

Nineteen persons from C-N, 16 from C-T, and 13 from HV scored above 40, for STAI-y1 (p=0.3), scores more than 40 indicate an anxiety state; 17 persons from C-N, 15 from C-T, and 8 from HV scored above 40 for STAI-y2 (p=0.05), scores more than 40 indicate an anxiety trait.

The PSQI score of all participants was inversely associated with the quality of the physical (r=–0.327 p=0.002) and mental (r=–0.455, p<0.001) component scores, while there were significant positive correlations between sleep quality and depression (Zung r=0.633, p<0.001), fatigue (r=0.377, p<0.001), state anxiety (r=0.484, p<0.001), and trait anxiety (r=0.467, p<0.001).

The age at testing was not related to sleep quality (r=0.105, p=0.323). In addition, gender (p=0.295), education (p=0.307), marital status (p=0.223), and gastrointestinal symptoms (p=0.403) were not related to sleep quality.
DISCUSSION

Data from this study indicated that sleep disorders are common in untreated celiac disease and should be considered a symptom of the disease. Sleep does not improve with a gluten-free diet, although the score tended to decrease, but did not reach those of the non-celiac volunteers. In detail, in celiac patients, all items explored by the PSQI but one — sleep duration — are impaired in comparison with volunteers. In celiac patients, sleep disorders are directly related to depression, anxiety, and fatigue and inversely related to quality-of-life scale scores. Age, gender, education, marital status, and the presence of gastrointestinal symptoms do not relate to the presence of sleep disorders.

Analysis of the SF36 questionnaire indicated that the scores on the PCS were low before starting a gluten-free diet, indicating limitations in physical/role functions, bodily pain, and general health, and these did not improve after treatment. The MCS score tended to decrease on a gluten-free diet. As a low MCS score suggests frequent limitations in psychosocial health, emotional problems, and reduced vitality (a fatigue construct), the data suggest that living with the limitations imposed by a gluten-free diet induces a worsening of psychosocial health and generates limitations in daily social and role activities.

This finding suggests that the sleep disorders are not related to the presence of gastrointestinal symptoms at diagnosis, and is why they did not improve on the diet, in contrast with the disappearance or improvement of most of the other symptoms.

The evaluation of the depression and anxiety scales scores in celiacs indicates that celiacs are more anxious and depressed than volunteers. In celiacs, however, a gluten-free diet did not induce any significant improvement in the score for any scale. This is in
contrast with the study of Addolorato, which found a significant improvement in state anxiety, but not depression, after one year of a gluten-free diet. One possible explanation is that celiacs from Addolorato study were evaluated after one year of gluten free diet. Our celiacs have been evaluated after an average of six years from diagnosis. This different time lapse might have played a role for the persistence (or renewal) of anxiety in our celiacs on gluten free diet.

The present study has the limit of a comparison with general population controls. On the other hand, a comparison with other chronic diseases is anyway unfeasible for the peculiar characteristics of celiac disease, the limitations imposed by gluten free diet and the disappearance of symptoms after some time from the beginning of the diet. However, the study was designed to reduce the effect of this limitation. The PSQI was administered at time of the first visit, hence when the person offering to the CD center had not yet received any previous CD diagnosis. The selection of any other GI disease as control group would have raised the problem of comparability because common GI diseases most often are with a clinical presentation and a ‘disease status’ heavier that CD. Finally, the metabolic status of the treated group was much better that one of the untreated group. Thus, the data indicate at least that sleep disorders in celiac disease are not fully controlled after six-years of gluten-free diet despite of a substantial improvement of the metabolic status.

In conclusion, our study confirms previous observations of a poor quality of life in celiacs both before and after diet treatment. For the first time, our findings indicate that sleep disorders are a frequent complaint in celiacs and should be added to the wide
spectrum of symptoms and signs of CD. Studies should determine if medical therapy that
improves sleep also improves the quality of life of celiac patients on a gluten-free diet.

Longitudinal studies are needed to confirm the present findings and to assess the effect of
gluten free diet.
REFERENCES


Table 1. Demographics of the study population (celiac-new C-N, celiac-treated C-T, healthy volunteer HV)

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<th>C-N</th>
<th>C-T</th>
<th>HV</th>
<th>p</th>
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<tr>
<td>Number of patients</td>
<td>30</td>
<td>30</td>
<td>30</td>
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<tr>
<td>Women/Men</td>
<td>20/10</td>
<td>20/10</td>
<td>20/10</td>
<td>1.000</td>
</tr>
<tr>
<td>Age at testing (years)</td>
<td>33.10±11.46</td>
<td>36.20±11.53</td>
<td>34±11.61</td>
<td>0.586</td>
</tr>
<tr>
<td>Education: high school or less/beyond high school</td>
<td>20/10</td>
<td>25/5</td>
<td>21/9</td>
<td>0.303</td>
</tr>
<tr>
<td>Married/Partnered (%)</td>
<td>56.66</td>
<td>63.33</td>
<td>53.33</td>
<td>0.956</td>
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Table 2. The percentage of scores indicating pathological sleep and the mean±SD of the PSQI results for celiac patients at diagnosis (celiac-new, C-N), on a gluten-free diet (celiac-treated, C-T), and volunteer (healthy volunteer, HV).

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<th>C-T</th>
<th>HV</th>
<th>p</th>
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<td>%PSQI pathological (&gt;5)</td>
<td>50%</td>
<td>33.3%</td>
<td>23.33%</td>
<td>0.093</td>
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<td>PSQI in the three groups</td>
<td>6.20±3.64</td>
<td>5.23±2.64</td>
<td>2.96±2.86</td>
<td>&lt;0.001</td>
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Table 3. The mean±SD of the scores of the modified Zung scale for depression, the VAS (1 to 10) for fatigue, and STAI-y1 and -y2 for state and trait anxiety in the study population (celiac-new C-N, celiac-treated C-T, healthy volunteer HV)

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<th>C-T</th>
<th>HV</th>
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<td>Modified Zung</td>
<td>34.23±6.73</td>
<td>31.40±7.19</td>
<td>25.40±5.85</td>
<td>&lt;0.001</td>
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<td>Fatigue VAS</td>
<td>6.13±2.54</td>
<td>5.5±2.17</td>
<td>3.43±2.36</td>
<td>&lt;0.001</td>
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<tr>
<td>STAI-y1</td>
<td>46.23±10.70</td>
<td>43.90±10.95</td>
<td>37.70±8.67</td>
<td>0.005</td>
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<tr>
<td>STAI-y2</td>
<td>42.90±8.10</td>
<td>42.73±9.55</td>
<td>36.23±8.02</td>
<td>0.004</td>
</tr>
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Figure 1. The mean±SD of the eight component scores of the SF36 questionnaire (physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional health, and mental health) and the mean±SD of the physical (PCS) and mental (MCS) component scales in celiac patients at diagnosis (celiac-new, C-N), on a gluten-free diet (celiac-treated, C-T), and volunteers (healthy volunteer, HV).
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Conflict of interest to declare: none

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Figure 1
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