Quality of life in clinically stable adult cystic fibrosis out-patients: Associations with daytime sleepiness and sleep quality

Anna Bouka, Henning Tiede, Linda Liebich, Rio Dumitrascu, Cornelia Hecker, Frank Reichenberger, Konstantin Mayer, Werner Seeger, Richard Schulz

Dept. of Sleep Medicine & Adult CF Service, University of Giessen Lung Center, Klinik-Str. 33, 35392 Giessen, Germany

Received 17 April 2012; accepted 10 June 2012
Available online 6 July 2012

KEYWORDS
Cystic fibrosis; Quality of life; Daytime sleepiness; Sleep quality

Summary
Background: Patients with cystic fibrosis (CF) may suffer from sleep disturbances and reduced health-related quality of life (HRQoL). However, the relationships of daytime sleepiness and sleep quality to HRQoL in CF have not yet been investigated.

Patients and methods: 55 adult CF out-patients free from a pulmonary exacerbation were prospectively enrolled in this study. Questionnaires were used to assess disease-specific HRQoL (German version of the revised Cystic Fibrosis Questionnaire for adults, CFQ18 + R), daytime sleepiness (Epworth Sleepiness Scale, ESS) and sleep quality (Pittsburgh Sleep Quality Index, PSQI). 30 age- and sex-matched healthy volunteers served as a control group.

Results: The prevalence of daytime sleepiness was higher in the CF than in the control group (ESS > 10; n = 11 [20%] vs. n = 2 [6.7%]; p < 0.01) as was reduced sleep quality (PSQI > 5; n = 21 [38.2%] vs. n = 1 [3.3%]; p < 0.01). Multiple regression analysis including age, gender, body mass index, lung function and pseudomonas status showed that higher PSQI scores significantly correlated with lower CFQ18 + R scores for vitality, emotional functioning, social, role, eating disturbances and digestive symptoms.

Conclusion: In clinically stable adult CF out-patients self-reported daytime sleepiness and poor sleep quality are more common than in age and sex-matched healthy controls. In addition, impaired sleep quality is related to reduced disease-specific HRQoL in CF.

© 2012 Elsevier Ltd. All rights reserved.

* This manuscript contains parts of the MD thesis of A. Bouka.
* Corresponding author. Tel.: +49 641 985 57030; fax: +49 641 985 42599.
E-mail address: Richard.Schulz@innere.med.uni-giessen.de (R. Schulz).
Introduction

Health-related quality of life (HRQoL) is a growing area of research in cystic fibrosis (CF). Reduced HRQoL in CF may be due to severe lung disease, pain or anxiety and depression.1–3 Furthermore, it may be related to gender-specific perceptions of physical and mental health, i.e. females with CF have been observed to report lower HRQoL.4 Working ability, socioeconomic status, race and ethnicity may also play significant roles in this context.5,6 Various sleep disturbances can occur in CF. Patients with severe airflow limitation may show REM sleep-related hypoventilation, hypoxemia and hypercapnia.7 Furthermore, bronchial mucus accumulation and reflux of gastric contents may cause episodes of nocturnal cough.8 Mood disorders such as anxiety and depression may also lead to problems with falling asleep and/or maintaining normal sleep. Finally, chronic pain can interfere with sleep quality in CF.9

In line with these assumptions, prior studies have found that CF patients may have disturbed sleep architecture, daytime sleepiness and impaired neurocognitive function.10–14 Patients with end-stage lung disease and frequent infective exacerbations seem to be mainly affected by these problems.

Against this background, poor sleep quality and excessive daytime sleepiness can be hypothesized to have a negative impact on HRQoL in CF, however, this has not yet been investigated. In the present study, we aimed to address this issue in a cohort of adult CF patients with the help of standard questionnaires evaluating disease-specific HRQoL, sleep quality and the degree of daytime sleepiness.

Patients and methods

Patient recruitment and assessment

The patients of the present study were investigated during an ambulatory visit to the Adult CF Service of the University of Giessen Lung Center, Germany between January and March 2012. All of them were older than 18 years of age and had a diagnosis of CF verified by sweat tests and/or genetic analysis. Their anthropometric parameters were determined, i.e. age, sex and body mass index (BMI). The current use of medications was evaluated, i.e. mucolytics (aerosolized DNase, hypertonic saline), antibiotics (nebulized tobramycin, colistin or aztreonam, oral azithromycin) and bronchodilators (β2-mimetics, parasympatholytic drugs). It was noted whether the patients were on long-term oxygen therapy or bilevel positive airway pressure therapy. All patients were investigated by pulmonary function tests and blood gas analysis from arterialized ear lobes. Finally, sputum specimens were obtained for microbiological analysis to determine if the patients’ airways were chronically colonized with Pseudomonas aeruginosa. If three consecutive sputum cultures showed these bacteria, the patients were judged to have a positive pseudomonas status.

Patients had to be in a stable clinical condition, i.e. those suffering from an ongoing or recent (i.e. within the last 4 weeks prior to study recruitment) pulmonary exacerbation were excluded. This was defined as clinical worsening (i.e. increased dyspnea, cough or sputum volume) accompanied by abnormal findings on chest examination (i.e. wheezing, inspiratory crackles) and/or a significant decrease in pulmonary function.15 Patients who had received a lung transplant were also not allowed to participate in the study.

During the study period, a total of 69 adult CF patients consecutively attended the outpatient clinic. Fifty-five of them were eligible for the study, the other 14 patients had to be excluded (4 patients had been transplanted and 10 patients presented with a pulmonary exacerbation or had just recovered from such an episode).

Healthy volunteers matched with the CF patients for age and gender and recruited by newspaper advertisement served as controls. The study protocol had been approved by the local ethics committee and all patients and controls had given their informed written consent.

Measures of quality of life, daytime sleepiness and sleep quality

Self-administered questionnaires were used to assess disease-specific HRQoL, daytime sleepiness and sleep quality. Disease-specific HRQoL was judged by the German version of the revised Cystic Fibrosis Questionnaire for adults (CFQ18 + R,16). This questionnaire consists of 50 items across 12 domains. Response choices generally include ratings of frequency and difficulty on a 4-point scale (1 = ‘always’ to 4 = ‘never’; 1 = ‘a lot of difficulty’ to 4 = ‘no difficulty’) or true/false responses (1 = ‘very true’ to 4 = ‘very false’). Scores are standardized on a 0- to 100-point scale, with higher scores representing better QoL. Cut-off values separating individuals with normal from those with abnormal scores have not yet been established on this instrument. However, for each domain of the CFQ18 + R mean scores for groups of patients considered to have varying degrees of CF disease severity have been reported.16,17 Based on this, the scores achieved on the various domains of the CFQ18 + R may be judged to be mildly, moderately or severely reduced.

The Epworth Sleepiness Scale (ESS,18) was used to assess the level of daytime sleepiness. In this questionnaire, the probability of falling asleep in different situations (n = 8) has to be rated on a 4-point scale (0 = ‘never’ to 3 = ‘high probability’). The maximal score of the ESS is 24 and values of >10 are considered to indicate excessive daytime sleepiness.

Finally, subjective sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI,19). The PSQI consists of 7 domains with a total of 19 questions. In each domain a score of 0–3 can be achieved. The scores of all domains are summarized (range: 0–21) with higher values indicating poorer sleep quality. Based on prior validations of the PSQI in psychiatric populations, a value of >5 may be regarded as evidence for poor sleep quality.

The CFQ18 + R refers to the past 2 weeks whereas the PSQI has a time window of 4 weeks. The questions of the ESS relate to the "last time" without any further specifications. None of the patients or controls who were asked to take part in the study refused to complete the questionnaires. The results of the questionnaires were analyzed by...
Data analysis

Data are presented as n/%, mean ± standard deviation or median ± interquartile range. First, the differences of the ESS and PSQI in the CF vs. the control group were evaluated and the anthropometric parameters of both groups were compared with t-test or Mann-Whitney test, as appropriate. With the same tests the mean scores of the different domains of the CFQ18 + R were compared in sleepy vs. non-sleepy patients (ESS > 10 vs. ≤ 10) and those with poor vs. good sleep quality (PSQI > 5 vs. ≤ 5).

Then, bivariate correlations between the scores on the ESS and PSQI and those of the different domains of the CFQ18 + R were calculated (Pearson’s correlation or Spearman’s rho, transformed before further analysis. Afterward, linear regression analysis were named “adjusted”, SPSS 19.0 was used for calculating statistics. A p-value of <0.05 was regarded as statistically significant.

Results

Characteristics of patients and controls

The patient characteristics are summarized in Table 1. The mean age of the 55 patients enrolled was in the mid-thirties with almost equal portions of males and females. On an average, the patients had relatively well-preserved nutritional status (i.e. a BMI >20 kg/m²) and moderately reduced pulmonary function. The majority of them were chronically infected with P. aeruginosa and regularly inhaled bronchodilators and antibiotics. About half of the patients inhaled mucolytics and received oral azithromycin as related to previous validations of this instrument.16,17 On almost all domains, patients who felt sleepy or had poor sleep quality had lower scores. In sleepy vs. non-sleepy patients, statistically significant differences were observed for the vitality (p < 0.01), emotional functioning, role and eating disturbances domains of the CFQ18 + R (p < 0.05, respectively). For patients with poor vs. good sleep quality this was the case for the emotional functioning and social domains of the CFQ18 + R (p < 0.01 and <0.05, respectively).

Daytime sleepiness/poor sleep quality in CF vs. controls

On an average, the scores on the ESS and PSQI were significantly higher in the CF than the control group (ESS: 7.5 ± 3.9 vs. 6.0 ± 2.7, p < 0.05; PSQI: 5.1 ± 3.3 vs. 2.8 ± 1.4, p < 0.01). 11 CF patients (20%) were considered to be sleepy (ESS > 10) and 21 [38.2%] to have reduced sleep quality (PSQI > 5). In contrast, daytime sleepiness and poor sleep quality were less frequently observed in the control group (n = 2 [6.7%] with ESS > 10 and n = 1 [3.3%] with PSQI > 5, p < 0.01 for each comparison with the CF group).

Health-related quality of life in CF

Fig. 1 shows the results of the CFQ18 + R in the patients studied. When looking at the patient cohort as a whole, the domains of the CFQ18 + R showed moderate score reductions as related to previous validations of this instrument.16,17 On almost all domains, patients who felt sleepy or had poor sleep quality had lower scores. In sleepy vs. non-sleepy patients, statistically significant differences were observed for the vitality (p < 0.01), emotional functioning, role and eating disturbances domains of the CFQ18 + R (p < 0.05, respectively). For patients with poor vs. good sleep quality this was the case for the emotional functioning and social domains of the CFQ18 + R (p < 0.01 and <0.05, respectively).

Relation of daytime sleepiness/poor sleep quality to health-related quality of life in CF

In general, daytime sleepiness as determined by the ESS was not linked to HRQoL in the patients investigated. After adjustment for age, gender, BMI, lung function and pseudomonas status, the only correlation which remained significant between the ESS and the CFQ18 + R scores was that of the vitality domain (r = −0.43, p < 0.01).

In contrast, poor sleep quality was more closely related to reduced HRQoL in CF. On multivariate regression analysis, statistically significant inverse correlations between
the PSQI and the CFQ18 + R scores were observed for the vitality, emotional functioning, social, role, eating disturbances and digestive symptoms domains (Table 2). There were no significant correlations between the PSQI scores and those on the physical functioning, weight and respiratory symptoms domains of the CFQ18 + R.

Discussion

In the present study, we observed that compared with age- and sex-matched healthy controls daytime sleepiness and poor sleep quality were more frequently encountered in clinically stable adult CF out-patients. Every fifth of these patients felt sleepy and every third reported reduced sleep quality. These data are in line with earlier reports investigating daytime well-being and sleep quality in CF.10–14

Evaluation of disease-specific HRQoL by the CFQ18 + R showed that our patients had moderate impairments in the domains of this questionnaire with more pronounced changes in those patients who were sleepy or had poor sleep quality.

Further statistical analysis revealed that daytime sleepiness as evaluated by the ESS was not significantly related to HRQoL in the CF patients investigated. However,

### Table 2

<table>
<thead>
<tr>
<th>CFQ18 + R domain</th>
<th>Correlation coefficients</th>
<th>Unadjusted p-value</th>
<th>Standardized coefficients</th>
<th>Adjusted p-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>−0.205</td>
<td>0.137</td>
<td>−0.255</td>
<td>0.074</td>
<td>−5.386/0.262</td>
</tr>
<tr>
<td>Vitality</td>
<td>−0.429</td>
<td>0.001</td>
<td>−0.463</td>
<td>0.001</td>
<td>−4.661/1.281</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>−0.598</td>
<td>&lt;0.001</td>
<td>−0.655</td>
<td>&lt;0.001</td>
<td>−5.711/−2.701</td>
</tr>
<tr>
<td>Social</td>
<td>−0.293</td>
<td>0.032</td>
<td>−0.336</td>
<td>0.022</td>
<td>−3.871/−0.309</td>
</tr>
<tr>
<td>Role</td>
<td>−0.259</td>
<td>0.061</td>
<td>−0.336</td>
<td>0.020</td>
<td>−0.080/−0.007</td>
</tr>
<tr>
<td>Body image</td>
<td>−0.180</td>
<td>0.194</td>
<td>−0.212</td>
<td>0.086</td>
<td>−4.467/0.035</td>
</tr>
<tr>
<td>Eating disturbances</td>
<td>−0.310</td>
<td>0.023</td>
<td>−0.309</td>
<td>0.034</td>
<td>−0.076/−0.003</td>
</tr>
<tr>
<td>Treatment burden</td>
<td>−0.194</td>
<td>0.164</td>
<td>−0.201</td>
<td>0.145</td>
<td>−3.948/0.599</td>
</tr>
<tr>
<td>Health perceptions</td>
<td>−0.176</td>
<td>0.202</td>
<td>−0.225</td>
<td>0.099</td>
<td>−4.234/0.380</td>
</tr>
<tr>
<td>Weight</td>
<td>−0.092</td>
<td>0.507</td>
<td>−0.160</td>
<td>0.279</td>
<td>−0.072/0.022</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>−0.183</td>
<td>0.185</td>
<td>−0.256</td>
<td>0.069</td>
<td>−3.795/0.149</td>
</tr>
<tr>
<td>Digestive symptoms</td>
<td>−0.369</td>
<td>0.006</td>
<td>−0.361</td>
<td>0.008</td>
<td>−0.071/−0.011</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for age, gender, BMI, FEV<sub>1</sub>/VC and pseudomonas status.
it should be kept in mind that the ESS is a highly variable marker of daytime sleepiness as has for instance been shown in patients with obstructive sleep apnea.\textsuperscript{20} Furthermore, the different items of the ESS are linked to specific situations which may not have been encountered by the individual respondents.

A novel finding was that poor sleep quality was significantly related to certain aspects of reduced disease-specific HRQoL in CF even after adjustment for confounding variables such as age, gender, BMI, lung function and pseudomonas status. Higher scores on the PSQI correlated with lower scores on those domains of the CFQ\textsuperscript{18 + R} representing mental health (i.e. vitality, emotional functioning, social and role). Thus, it may be speculated that psychological factors such as anxiety and depression lead to reduced sleep quality in CF. In addition, it may be possible that pancreatic insufficiency or other gastrointestinal disease causing abdominal pain worsens sleep quality in CF. This is suggested by the observation that higher PSQI scores also correlated with lower CFQ\textsuperscript{18 + R} scores for eating disturbances and digestive symptoms.

Somewhat unexpectedly, the PSQI scores did not significantly correlate with those of the physical functioning, weight and respiratory symptoms domains of the CFQ\textsuperscript{18 + R}. However, this may be explained by the fact that our patients had on average almost normal body weight and moderately reduced pulmonary function. Furthermore, it may be related to the design of the study excluding those CF patients with ongoing or recent pulmonary exacerbations.

It should be acknowledged that, based on our data, it is not possible to establish cause–effect relationships between poor sleep quality and reduced HRQoL in CF. In order to clarify this issue, future studies could for example perform randomized, controlled therapeutic interventions to improve sleep quality and then re-evaluate HRQoL in these patients. Based on the results of our study, we propose that psychological support may be of special value to improve sleep quality in CF. Nutritional counseling aimed at reducing abdominal discomfort and pain may be another option.

Our study has some possible limitations. First, we did not perform polysomnographic studies and therefore could not gain insight into the patients' sleep architecture, i.e. objective sleep quality. For the same reason, it is also not possible to judge if poor sleep quality was due to breathing anomalies while asleep. The latter point is of considerable interest as a recent study reported that CF patients with nocturnal oxygen desaturations have impaired quality of life.\textsuperscript{21} Second, we did not carry out multiple sleep latency tests which would have enabled us to rate the degree of daytime sleepiness of the patients. Third, it should be realized that the ESS and PSQI have not yet been validated in CF. Nevertheless, we employed the cut-off values which have been reported in other patient populations to separate individuals with vs. without daytime sleepiness/poor sleep quality to describe our findings. Finally, QoL was not evaluated in the control group. However, it must be considered that the questionnaire used in the present study, i.e. the CFQ\textsuperscript{18 + R}, is specifically designed for use in people with CF. Thus, to compare QoL in CF and controls, it would have been necessary that both groups responded to a generic QoL questionnaire such as the SF-36.

We conclude that self-reported daytime sleepiness and impaired sleep quality are more common in clinically stable adult CF out-patients than in age- and sex-matched healthy controls. In addition, poor sleep quality is related to reduced disease-specific HRQoL. Although these observations clearly need further study, they do suggest that more attention should be paid to sleep-related symptoms in individuals with CF.

Conflict of interest

None of the authors has any conflict of interest to disclose.

References


