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Sleep quality, daytime sleepiness and fasting insulin levels in women with chronic obstructive pulmonary disease

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Summary *Study objectives:* To test the clinical observations that patients with chronic obstructive pulmonary disease (COPD) have impaired sleep quality without excessive daytime sleepiness (EDS), and to analyse the aetiological factors.

Participants: Fifteen non-diabetic postmenopausal women with moderate to severe COPD and 20 community dwelling age-matched control women.

Measurements and results: Patients completed questionnaires, had a polysomnography and blood tests. Controls filled in the questionnaires. In the Basic Nordic Sleep Questionnaire, the average ($\pm$SD) scores for sleepiness (9.9 ± 3.0 in patients vs. 7.6 ± 3.2 in controls, $P = 0.025$, test range 4–20) and insomnia (18.3 ± 3.4 vs. 16.6 ± 4.4, $P = 123$, test range 7–35) were low. Although 53% had a good night's sleep seldom or never and 70% slept restlessly, only 33% felt tired in the mornings. Controls reported better sleep quality, less tiredness and sleepiness. With polysomnography, the total sleep time was 4 h 41 min $\pm$1 h 20 min in patients. Sleep was fragmented, the proportion of stage 1 sleep high and rapid eye movement (REM) latency delayed. Sleepiness correlated with fasting serum insulin levels ($r = 0.59$, $P = 0.027$) and body movements ($r = 0.52$, $P = 0.047$). In stepwise linear regression analyses, sleepiness was positively associated with insulin levels ($P = 0.025$) but not with body movements. Insulin explained 38.0% of the variance in the sleepiness score, when adjusted for body mass index (BMI).

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Conclusions: Despite short and fragmented sleep, non-diabetic patients with COPD did not have marked EDS. An association between fasting insulin and sleepiness suggests that insulin resistance is involved in EDS.

Introduction

Sleep quality is impaired in patients with chronic obstructive pulmonary disease (COPD).[1–3] Sleep fragmentation and arousals frequently occur during events of desaturation.[2,4] Fragmented sleep and frequent arousals lead to daytime sleepiness both in healthy normal volunteers[5] and in patients with sleep-disordered breathing.[6,7] The scarce data regarding daytime sleepiness in patients with COPD is contradictory.[1,8] According to our clinical observations, patients with moderate to severe COPD without acute exacerbation do not complain about excessive daytime sleepiness (EDS) as patients with obstructive sleep apnoea syndrome (OSAS) do.

Our aim was to test the hypothesis that ambulatory patients with moderate to severe COPD have impaired sleep quality but do not report EDS. We also aimed to analyse the possible aetiological factors. Therefore, we investigated subjective sleepiness, subjective and objective sleep quality, nocturnal arterial oxygen saturation and transcutaneous partial carbon dioxide pressure in women with COPD. Because plasma insulin levels are higher in patients with OSAS than in obese controls possibly due to hypoxia-related nocturnal increases in sympathetic activity,[9] we also investigated relationships between serum fasting insulin levels and the above-mentioned variables.

Participants and methods

Patient selection

We recruited 15 postmenopausal women with COPD, one of them also presenting with a marked restrictive component of ventilatory impairment. The study population comprised of consecutive female patients visiting at our outpatient clinic in the department of pulmonary medicine and fulfilling the study criteria. Demographic and respiratory characteristics of the patients are presented in Table 1. Patients with forced expiratory volume in one second (FEV_1) less than 65% of predicted value, and a history of episodic or constant daytime hypoxaemia ($PaO_2 < 10.0$ kPa) and/or hypercapnia ($PaCO_2 > 6.0$ kPa) assessed by arterial blood gas analyses were included. All patients were on an optimal medication and had been in a stable clinical condition for at least a month prior the study. Only current non-smokers were included in order to avoid the effect of smoking and nicotine on sleep, control of breathing and other factors. Ten patients were former smokers. Two of them had quitted smoking at least 6 months but less than one year before the present study. The others had stopped smoking 4–27 years before the study. Two out of five life-long non-smokers had alpha-1-antitrypsin deficiency. The other three non-smokers had been exposed for passive smoking and one of them also had work-related exposure for irritants more than 10 years likely to contribute to COPD. The mean of pack-years was 8.8 years (range 0–50). The postmenopausal status was verified by an increase in serum concentration of follicle-stimulating hormone over 30 IU/L. None of the patients had hot flushes or other menopausal symptoms.

The exclusion criteria were heart diseases (except cor pulmonale), malignancies, psychiatric, and neurological diseases, diabetes mellitus, uraemia, untreated hypothyroidism, current smoking, long-term oxygen therapy, use of postmenopausal hormone replacement therapy, and use of any medication likely to influence sleep or vigilance

Table 1 Demographic and respiratory data of patients.

Patient characteristics, $n = 15$	Mean ± SD or median (range)
Age (years)	67.5 ± 6.0
BMI (kg/m^2)	26.9 ± 4.9
FEV_1 (L)	0.73 (0.25–1.8)
FVC (L)	1.3 ± 0.45
FEV_1 (%)	36 ± 12
FVC (%)	46 ± 16
FEV%	63 ± 14
Mean SaO_2 during sleep (%)	88.6 ± 9.4
Nadir SaO_2 during sleep (%)	84.8 (46.8–90.1)
Mean $tcCO_2$ during sleep (kPa)	6.3 ± 1.2

Data presented as mean ± SD or median (range). BMI, body mass index, FEV_1, forced expiratory volume in one second, FVC, forced vital capacity, FEV_1(%), forced expiratory volume in one second percent of predicted value, FVC (%), forced vital capacity percent of predicted value, FEV%, 100 × (FEV_1/FVC), SaO_2, arterial oxyhaemoglobin saturation, $tcCO_2$, transcutaneous carbon dioxide partial pressure.

such as benzodiazepines, psychostimulants, or antidepressants.

Controls

For the purpose of the study, questionnaire data were also collected from 20 postmenopausal controls matched for age (mean age $\pm$ SD 67.5 $\pm$ 3.4 years). All controls were community dwelling females without self-reported or doctor-diagnosed COPD or OSAS.

Each participant gave her written informed consent. The study protocol was approved by the Joint Commission on Ethics of Turku University and Turku University Central Hospital.

Measurements

In the evening prior the sleep study, patients were interviewed and a routine physical examination was performed. Since neither patients nor controls had tendency to doze off involuntarily, the Basic Nordic Sleep Questionnaire[10] was preferred to the Epworth Sleepiness Scale, which focuses on the probability of falling asleep in various situations.[11] The Basic Nordic Sleep Questionnaire surveys perception of usual sleep quality, sleep latency, and the number of awakenings per night and naps per day. Each patient also rated a 10-cm visual analogue scale (VAS) with a statement "I am happy with my sleep quality", score = 0 indicating "completely agree" and score = 10 indicating "completely disagree". Frequency of morning headaches was inquired. Sleepiness was assessed by four questions and insomnia by seven questions adapted from the Basic Nordic Sleep Questionnaire.[10] Sleepiness scores range from 4 to 20 points, insomnia scores from 7 to 35, the higher scores indicating more problems with sleepiness or insomnia.

In the morning after the sleep study, all patients completed a 14-item questionnaire relating to their perceptions of the preceding night's sleep. This questionnaire allowed the comparison of subjective and objective sleep quality. Questions were related to initiation and maintenance of sleep (for example, perceptions of sleep latency, frequency of arousals), events during sleep (for example, restlessness), sleep-related daytime symptoms (for example, naps), and issues possibly disturbing sleep (for example, dyspnoea, sweating). Patients completed all questionnaires in the presence of one of the investigators.

An overnight polysomnography included monitoring of electroencephalogram (EEG; C3/A2 and C4/A1), electro-oculogram, and submental electromyogram. Arterial oxyhemoglobin saturation (SaO_2) was measured with pulse oximeter using a finger probe (Ohmeda Biox 3700 Pulse Oximeter, BOC Health Care, USA). Transcutaneous partial carbon dioxide pressure ($tcCO_2$) was measured with TCM3 device (TINA® Transcutaneous PO_2/PCO_2 Monitoring System, Radiometer, Copenhagen, Denmark). The sensor was heated up to 43 °C. Movements during sleep were monitored with a static-charge-sensitive bed.[12–14] Quantitative movement analysis, SaO_2 analysis, and carbon dioxide partial pressure analyses were determined with analyse modules (UniPlot®, Unesta, Turku, Finland). The presence of airflow was determined via nasal prongs connected to continuous positive airway pressure device used in diagnostic mode (Sullivan Autoset®, ResCare Limited, Sydney, Australia). Biosignals were recorded and saved on a PC hard disk using UniPlot software (UniPlot®, Unesta, Turku, Finland) with sampling frequency of 250 Hz per channel and with y-resolution of 12 bytes.

Sleep stages were scored according to standard criteria[15] and expressed as percentage of total sleep time. Sleep efficiency was defined as percentage of sleep during the sleep period time. Arousal was defined as an appearance of EEG-alpha activity for longer than 3 s.[16]

In the morning after a sleep study, flow-volume spirometry (Vitalograph Compact II, Vitalograph Ltd, Buckingham, England) was assessed and blood samples were collected between 7 and 9 a.m. after an overnight fast. Serum fasting insulin was determined with a Phadeseph® Insulin RIA kit (Pharmacia, Uppsala, Sweden).

Controls completed the Basic Nordic Sleep Questionnaire but did not have sleep studies or blood tests.

Statistical analyses

Pearson correlation coefficients were used in parametric cases and Spearman correlation coefficients in non-parametric cases to assess the association between two numeric measurements. Linear regression analysis was used to evaluate the associations between insulin and several variables or sleepiness and other variables. Body mass index (BMI) was entered into the stepwise linear regression analysis model. Wilcoxon test was used in between group comparisons. Data is presented as mean $\pm$ SD when applicable or median (range). In all tests, $P < 0.05$ was considered significant. Statistical computing was performed with SAS statistical package (version 8.01, SAS Institute, Cary, NC).

Results

Patients were hypoxaemic and their average of $tcCO_2$ was 6.3 ± 1.2 kPa during sleep compatible with COPD (Table 1).

Overall subjective sleep quality

Basic Nordic Sleep Questionnaire: In patients with COPD, the average of sleepiness score of the Basic Nordic Sleep Questionnaire (9.9 ± 3.0, test range 4–20) was low although higher than in controls (7.6 ± 3.2, $P = 0.025$). The averages of the insomnia scores (18.3 ± 3.4 vs. 16.6 ± 4.4, test range 7–35) did not differ ($P = 0.123$). A good night's sleep seldom or never was reported by 53% of the patients and by 10% of controls ($P = 0.006$). Restless sleep was reported by 73% vs. 15% ($P < 0.001$) and feeling tired every or almost every morning by 33% vs. 5% ($P = 0.032$). Neither patients nor controls had tendency to doze off involuntarily. The frequency of morning headaches did not differ between the groups. Four out of 15 (27%) patients and 2 out of 20 controls (10%) had morning headaches ($P = 0.211$). Detailed data is presented in Fig. 1.

VAS: Patients were moderately satisfied with their subjective sleep quality when measured with a VAS (mean score 4.0 ± 3.3). Subjective sleep quality correlated with forced expiratory volume (Pearson $r = 0.64$, $P = 0.014$).

Subjective sleep quality during the study night

Patients reported that they fell asleep rather soon, slept moderately well, slept as usual, had some nocturnal movements, woke up several times during night, woke up earlier than usual, but felt rather alert in the morning after their sleep study. Five out of 15 patients reported having naps during the preceding day. They had no specific complaints (pains, cough, etc.) disturbing their sleep.

Objective sleep quality during the study night

During the study night, the mean total sleep time was less than 5 h and sleep efficiency was poor (Table 2). The proportion of stage 1 sleep was high. Rapid eye movement (REM) latency was delayed. Sleep was fragmented (Fig. 2) but EEG arousal index was low. Total sleep time correlated with sleep efficiency (Pearson $r = 0.94$, $P < 0.0001$) as expected. Any of the variables of overnight sleep recording did not correlate with spirometric results.

Sleepiness and fasting insulin concentrations

One serum sample was missing and therefore serum insulin concentrations were assessed only in 14 patients. None of the patients had diabetes mellitus. Their mean fasting serum insulin

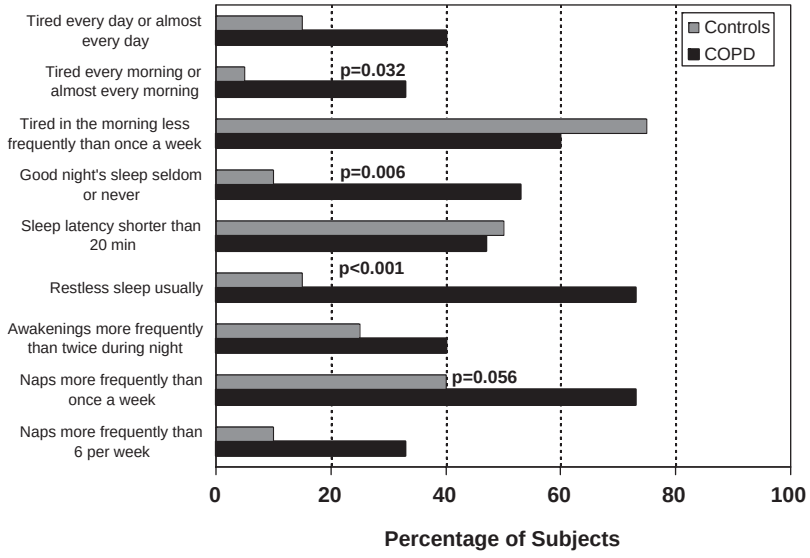

Figure 1 Subjective sleepiness and sleep quality, $n = 15$ for patients with chronic obstructive pulmonary disease (COPD) and $n = 20$ for age- and gender-matched controls. Data were derived from the Basic Nordic Sleep Questionnaire.[10] Data are presented as percentage of subjects.

Table 2 Sleep recording data.

Objective sleep quality, $n = 15$	
TST (min)	281 ± 80
Sleep efficiency (%)	70.0 (32.7–91.3)
WASO (% of sleep period time)	31.3 (4.5–62.8)
Arousal index (# per hour)	1.0 (0.2–11.4)
BM per hour of sleep	6.3 (1.0–116.6)
MA per hour of sleep	9.5 ± 6.9
S1 latency (min)	11.5 (2.5–90.5)
S2 latency (min)	22.0 (11.0–144.5)
SWS latency (min)	34.5 (1–220)
REM latency (min)	138 (62.5–285.5)
Stage S1 sleep (% of TST)	26.3 (10.0–88.0)
Stage S2 sleep (% of TST)	28.2 ± 14.7
SWS (% of TST)	25.2 ± 9.8
REM sleep (% of TST)	12.2 ± 9.2
Stage shifts	16.9 ± 4.0

Data presented as mean ± SD or median (range). BM, body movements, MA, movement arousals, REM, rapid eye movements, SWS, slow wave sleep (sleep stages 3 and 4), TST, total sleep time, WASO, wakefulness after sleep onset.

concentration was 12.0 ± 4.2 mU/L (reference range 5–20 mU/L, interassay coefficient of variation 4.6% at control sample level of 12.4 mU/L). One patient had her insulin level above the upper limit of reference ranges, the value being 22 mU/L.

In univariate analyses, sleepiness score correlated with insulin levels (Pearson $r = 0.59$, $P = 0.027$; Fig. 3) and body movements (Pearson $r = 0.52$, $P = 0.047$). Sleepiness score or insulin levels did not correlate significantly with age, BMI, lung volumes, apnoea-hypopnoea index, insomnia score, being tired in the morning or with VAS score of the subjective sleep quality or any measures of the objective sleep quality except that insulin correlated with percentage of time spent in stage 2 sleep (Pearson $r = 0.53$, $P = 0.047$). When adjusted for age and BMI, there tended to be positive associations in linear regression analyses between insulin and SaO_2nadir during sleep overall ($P = 0.086$) and during slow wave sleep (SWS; $P = 0.091$), between insulin and SaO_2mean during stage 2 ($P = 0.050$) and stage 4 sleep ($P = 0.058$), and between insulin

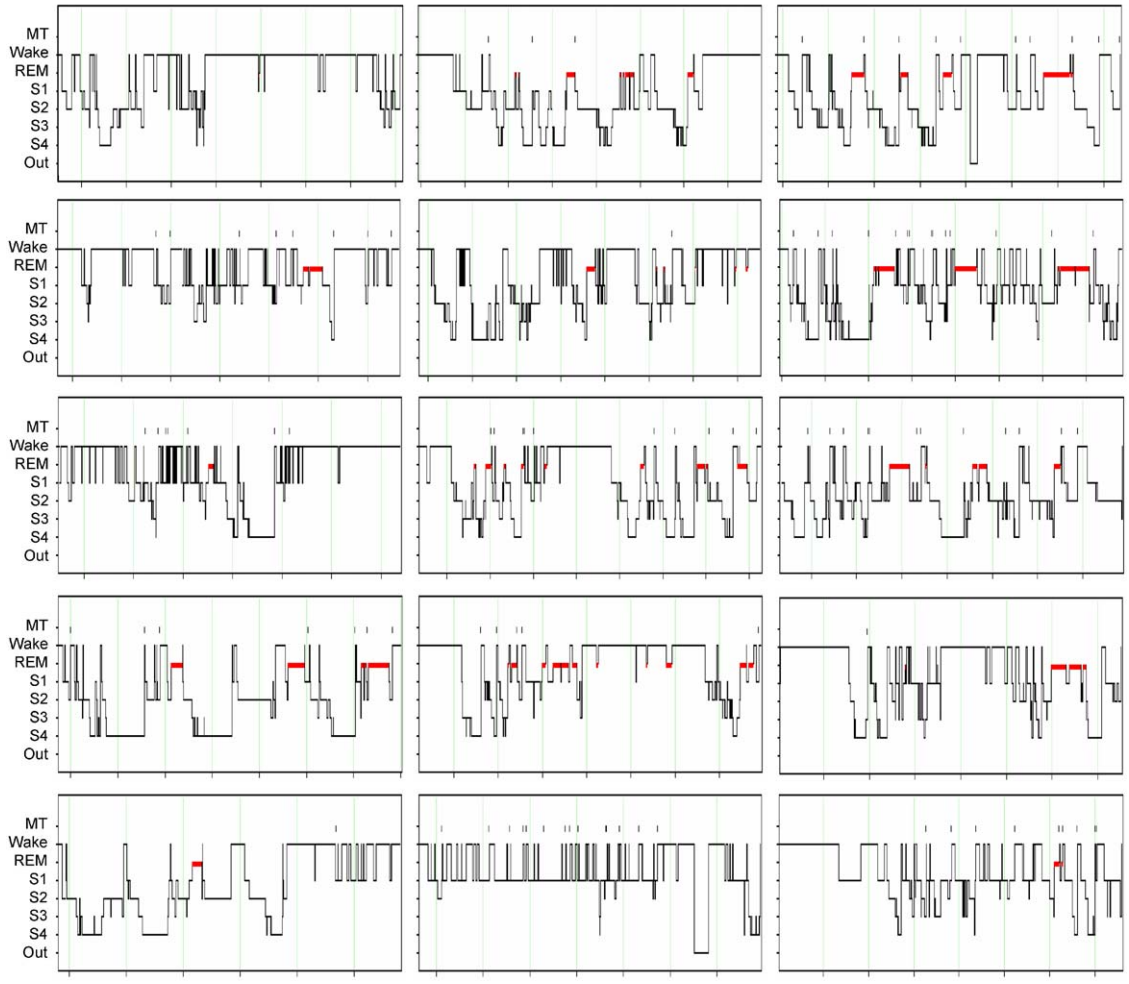

Figure 2 Hypnograms of all the 15 patients. Their sleep structure is remarkably destroyed. MT, movement time, REM, rapid eye movement sleep, S1, sleep stage 1, S2, sleep stage 2, S3, sleep stage 3, S4, sleep stage 4.

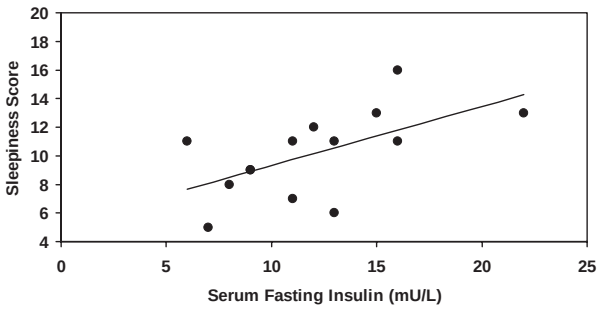

Figure 3 Association between sleepiness score and serum fasting insulin concentration in postmenopausal women with chronic obstructive pulmonary disease ($n = 14$, Pearson $r = 0.59$, $P = 0.027$). Test range for sleepiness score is 4–20.

and $tcCO_2$ during sleep overall ($P = 0.052$), during stage 1 sleep ($P = 0.057$) and during SWS ($P = 0.056$).

In stepwise linear regression analyses with BMI entered into the model, sleepiness was positively associated with insulin levels ($P = 0.029$), but not with body movements ($P = 0.151$). Insulin level explained 38.0% of the variance in the sleepiness score. BMI did not explain the variance in the sleepiness score (6.2%, $P = 0.434$). Insulin level was positively associated with percentage of stage 2 sleep ($P = 0.005$) and with sleepiness ($P = 0.004$). Percentage of stage 2 sleep explained 29.0% and sleepiness 47.6% of the variance in the insulin levels. BMI tended to explain insulin levels (25.4%, $P = 0.095$). Previous smoking (pack-years) did not explain sleepiness ($P = 0.149$) or insulin levels ($P = 0.496$).

Discussion

Our postmenopausal women with moderate to severe COPD and with mean total sleep time less than 5 h did not have major daytime sleepiness although felt somewhat tired. None of our patients was diabetic and only one had slightly increased fasting concentration of serum insulin. However, sleepiness was associated with fasting insulin levels but not with nocturnal hypoxaemia, arousals, or sleep fragmentation, which are the conventional predictors of EDS in healthy subjects or patients with obstructive sleep apnoea.[7,17,18] The results suggest that chronic lung disease modifies the pathophysiology of EDS.

Objective sleep quality in COPD

The objectively verified poor sleep quality (short total sleep time, sleep fragmentation, remarkably little deep sleep) and lack of EDS is contradictory to observations in healthy subjects, in whom partial or total sleep deprivation for one night[19] or for consecutive nights[20] results in increased daytime sleepiness. We were neither able to confirm the observations that number of EEG arousals, shifts from other sleep stages to stage 1 sleep or wake, nor the percentage of stage 1 sleep correlates with daytime sleepiness.[21] In our patients, number of EEG arousals was low but stage shifts were frequent, and the percentage time spent awake or in stage 1 sleep was high. The differences in study populations between our study (females with COPD) and that of Stepanski and co-workers[21] (patients with sleep apnoea, with periodic leg movements or with insomnia and healthy volunteers without sleep complaints) may explain the discrepancy.

On the other hand, our findings are in line with those of Orr and co-workers, who did not observe any significant daytime sleepiness in male patients with COPD.[8] Despite short total sleep times (mean 4.3 h), their multiple sleep latency test (MSLT) results were within normal range. Similar total sleep times (mean 4.7 h) were observed by us but we did not perform MSLT. However, the rather long sleep latencies of our COPD patients would predict normal MSLT results, since the sleep latencies at night and during MSLT correlate positively.[18]

The short total sleep time in our patients falls in previously reported ranges from 3.5 to 4.7 h per night in COPD[1,2,8] However, the total sleep time was markedly shorter than in healthy elderly subjects in previous studies[19,22,23] or 7.0 ± 0.6 h reported by our controls. The percentage of wakefulness after sleep onset was higher than that in patients with COPD of Fleetham and co-workers[2] or in healthy postmenopausal women (mean age 56.3 years)[24] but similar to that of Cormick and co-authors. Because our patients spent most of the time in light sleep, arousals easily resulted in awakenings and thereby in lower arousal index than previously reported in healthy elderly people[19] or in patients with COPD.[1,2] The number of sleep-stage shifts per hour of sleep was high but is compatible with previous reports.[1,2] Sleep latency was comparable to those reported previously in the elderly people[19,22,23] or in our controls.

The percentage of sleep stage 1 was high and the percentage of REM sleep low consistent with previous observations in the elderly subjects,[19,22,23] or in patients with COPD.[1,2] Although the absolute time spent in slow wave sleep (SWS) or REM was very short, the percentage time did not differ from that of healthy elderly people.[22,23]

We were not able to demonstrate any association between objective sleep quality and pulmonary function tests or SaO_2 or $tcCO_2$ during sleep. This finding is consistent with a previous report that the extent of sleep disruption does not depend on hypoxaemia and is present also in normoxic patients with COPD.[3]

Subjective sleep quality and sleepiness

Patients reported to have a good night's sleep hardly ever and their sleep was restless. Surprisingly, they were satisfied with their overall sleep quality measured with VAS. Adaptation to poor sleep quality could explain this discrepancy. When asked with a more specified question, they reported poor sleep although failed to report that in a context of a more general question. Napping is common among retired elderly people. It was also quite frequent in our study population and tended to be more frequent than in controls. It is also remarkable that in the morning patients felt relatively alert despite their objectively poor sleep. Although patients with chronic pulmonary disease had fatigue, they did not have a compulsory tendency to fall asleep like patients with OSAS.

Insulin and sleepiness

Because sleep or respiratory variables did not give any explanation to the paradoxical finding of lack of sleepiness in the presence of poor sleep quality, it led us to seek other alternatives. Both obesity[25] and hypercytokinemia[9,26] have been linked with EDS. Typical for an advanced chronic pulmonary disease, our patients were non-obese, which might explain the lack of daytime sleepiness. However, sleepiness scores did not correlate with BMI. We did not measure cytokines. However, increased circulating levels of tumour necrosis factor-alpha and interleukin-6 have been reported in patients with COPD.[27] These cytokines are also known as sleep-promoting cytokines. Therefore, it is unlikely that different cytokine profiles in sleepy patients with OSAS and non-sleepy patients with COPD could explain the difference in their grade of alertness.

Insulin resistance is common in OSAS.[9] Data from both animal and human studies support an association between insulin levels and sleepiness. In rats, exogenous systemic administration of insulin promotes non-REM sleep but has little, if any effect on REM sleep.[28] Continuous intracerebroventricular infusion of insulin increases somnolence in rhesus monkeys.[29] Plasma insulin levels are associated with postprandial sleepiness in healthy female and male volunteers.[30] Fasting insulin reflects quite reliably insulin resistance.[31] Patients with sleep apnoea have higher fasting plasma insulin levels than BMI-matched obese controls.[9]

There are two major differences between patients with COPD and OSAS, which may affect insulin levels. First, patients with OSAS are often obese and obesity is a well-known risk factor for insulin resistance.[32] Second, in OSAS the changes in nocturnal oxygen saturation are abrupt while in COPD they usually are more shallow and constant, which may enable a better adjustment of body homeostasis.

Limitations of the study

We acknowledge several limitations of our study design. First, we did not have an adaptation night for being monitored in a sleep laboratory. However, our findings of objective sleep quality are consistent with previous studies in patients with COPD.[1,2,8] Patients also reported that they slept during the study night as usual. Therefore, any major bias due to possible first night effect seems unlikely. Second, our control group did not have sleep studies, blood tests or pulmonary function tests. However, these issues are unlikely to disprove our major finding of absence of EDS in our study population. Although the absence of COPD in controls was based on questionnaire data, it is not plausible that any of them would have undiagnosed moderate to severe COPD like our patients. Third, the number of study participants is small and all are females. On the other hand, the fact that all the patients are women may stabilize the observations. Significant findings even in this small population suggest strong association.

Conclusions

Our non-diabetic patients with moderate to severe COPD had a remarkably short total sleep time and fragmented sleep, but did not have major EDS although had fatigue to some extent. An association between fasting serum insulin level and sleepiness suggests that insulin resistance may play a role in EDS. Lack of insulin resistance may therefore explain absence of EDS in most patients with COPD. Whether the observed correlation between fasting insulin levels and EDS would also be extrapolated to males, younger patients with COPD or those with more severe degrees of EDS in obese patients with diabetes mellitus or with OSAS, remains to be elucidated.

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