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ARTICLE

Disturbed subjective sleep characteristics in adult patients with long-standing type 1 diabetes mellitus

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Abstract
Aims/hypothesis Decreased sleep duration and/or impaired sleep quality negatively influence glucoregulation. The aim of this study was to assess subjective sleep characteristics in patients with type 1 diabetes, to relate sleep characteristics to long-term glycaemic control and to assess possible risk factors for impaired sleep.
Methods We studied 99 adult patients with type 1 diabetes (55 men, 44 women, duration of diabetes 26.9±1.2 years) and 99 age-, sex- and BMI-matched non-diabetic controls. Subjective sleep characteristics were assessed by validated questionnaires, i.e. Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale and the Berlin Questionnaire. Glucoregulation was assessed by HbA_{1c} values. Clinical variables were obtained from medical charts. Depression was assessed by the Hospital Anxiety and Depression Scale (HADS). Peripheral polyneuropathy was assessed by neurological examination and quantitative sensory testing.
Results Of the patients with type 1 diabetes, 35% had subjective poor sleep quality compared with 20% of the control participants (p=0.021). A higher proportion of the patients with type 1 diabetes were at increased risk for obstructive sleep apnoea (OSA) (17.2% vs 5.1%, p=0.012). There was no significant association between individual sleep characteristics and HbA_{1c} values. On logistic regression analysis, the HADS depression score, presence of peripheral polyneuropathy, habitual snoring and other sleep disturbances (e.g. hypoglycaemia) were independently associated with poor sleep quality.
Conclusions/interpretation Adult patients with long-standing type 1 diabetes mellitus have disturbed subjective sleep quality and a higher risk for OSA compared with control participants. Subjective sleep disturbances are part of the complex syndrome of long-standing type 1 diabetes.

Keywords Glucoregulation · Sleep · Sleep disorders · Type 1 diabetes mellitus

Abbreviations

BQ	Berlin Questionnaire
ESS	Epworth Sleepiness Scale
HADS	Hospital Anxiety and Depression scale
mTCNs	Modified Toronto Clinical Neuropathy Scale
OSA	Obstructive sleep apnoea
PSQI	Pittsburgh Sleep Quality Index
RLS	Restless leg syndrome

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Introduction

Patients with type 2 diabetes report sleep disturbances more frequently than individuals from the general population [1, 2]. This is relevant for glucoregulation, as epidemiological [3–5] and experimental studies [6–8] have shown that reduced sleep duration and/or decreased sleep quality markedly reduce glucose tolerance and insulin sensitivity.

There are only a few studies on sleep characteristics in patients with type 1 diabetes.

Jauch-Chara et al. [9] reported a trend towards less slow wave sleep in 14 non-hypoglycaemic adult patients with type 1 diabetes. Children with type 1 diabetes had more disrupted sleep [10, 11] and more sleep disorders [12] than healthy children. Conversely, in adult patients with type 1 diabetes, partial sleep deprivation, even during only a single night, reduced peripheral insulin sensitivity by 21% [13]. Subjective sleep characteristics and their relation with glucoregulation have not been studied in adult patients with type 1 diabetes.

We hypothesised that adult patients with type 1 diabetes may have alterations in subjective sleep characteristics, assessed by validated sleep questionnaires, compared with healthy controls. In addition, we hypothesised that subjective sleep disturbances would be associated with impaired glucoregulation. Therefore, the aim of the present study was: (1) to assess subjective sleep characteristics by validated sleep questionnaires in adult patients with type 1 diabetes, compared with age-, sex- and BMI-matched non-diabetic controls; (2) to relate sleep characteristics to the quality of glycaemic control, i.e. HbA_{1c} values; and (3) to assess possible risk factors for impaired sleep characteristics in adult patients with type 1 diabetes.

Methods

Participants

We included 99 consecutive patients with type 1 diabetes mellitus (55 men, 44 women) attending the outpatient clinic of the Leiden University Medical Center, and 99 age-, sex- and BMI-matched non-diabetic controls recruited by advertisement. Every patient with type 1 diabetes was individually matched with one non-diabetic healthy control for age, sex and BMI.

Exclusion criteria for both groups were: (1) previously diagnosed sleep disorders; (2) psychiatric disorders and/or use of psychotropic medication; (3) pregnancy or lactation; (4) working in nights shifts in the last 3 months; (5) travelling across time zones in the previous month; (6) age <18 years; (7) other endocrine disorders; (8) neuropathy caused by other conditions than type 1 diabetes; (9) chronic co-morbidity, other than peripheral neuropathy, associated with pain; and (10) chronic use of glucocorticoids.

The study was approved by the medical ethical committee of Leiden University Medical Centre and written informed consent was obtained from all participants prior to the study.

Study design

Patients and controls were asked to complete three validated sleep questionnaires—the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), and the Berlin Questionnaire (BQ)—that provide data on sleep quality, daytime sleepiness and the presence of sleeping disorders [14–16]. An additional questionnaire focused on duration and insulin management of type 1 diabetes, use of medication, co-morbidity, current smoking status and use of alcohol and coffee. Four questions aimed to identify restless legs syndrome (RLS), using the minimum criteria defined by the International RLS Study Group [17]. As depressive feelings may also affect sleep characteristics, anxiety and depression scores were assessed by the Hospital Anxiety and Depression scale (HADS) [18].

Sleep disturbances were identified by the answers of the ten possible encountered sleep disturbances of the PSQI questionnaire. The option ‘three times or more per week’ was taken as the affirmative answer. Habitual snoring was defined as a ‘yes’ answer to the three-item question ‘Do you snore’ in the BQ. The participants who answered ‘not known’ to this question were classified as non-snorers. We also included additional questions: ‘Has your sleep been disturbed by hypoglycaemia in the past month? Has your sleep been disturbed by hyperglycaemia in the past month?’ The following four options were provided: ‘never’; ‘less than once per week’; ‘once or twice per week’; and ‘three times or more per week’.

The following data were obtained from medical records for the 12 months preceding the current study. Microvascular complications were defined by the presence of: (1) retinopathy identified by retinal photography, detailed ophthalmologic examination and/or previous laser therapy; or (2) nephropathy identified by increased urinary albumin-to-creatinine ratios (men >2.5 μg/μmol, women >3.5 μg/μmol). Macrovascular complications were defined by objective documentation of coronary artery disease (diagnostic cardiac exercise test, coronary angiography, documented myocardial infarction and/or coronary artery bypass surgery or percutaneous coronary interventions), cerebral vascular disease (documented focal neurological findings supported by appropriate imaging studies) or peripheral vascular disease defined by reduced ankle–arm index or angiography. Hypertension was defined as systolic blood pressure ≥135 mmHg or diastolic blood pressure ≥85 mmHg at multiple

occasions or treatment with antihypertensive medication. All patients had HbA_{1c} data obtained within the previous 3 months. An HbA_{1c} value of 7.5% (58 mmol/mol) was taken as the cut-off point dividing well-controlled vs moderate-to-poorly controlled patients.

The presence of peripheral polyneuropathy in the lower extremities was assessed by a single researcher (M. van Dijk), both in all type 1 diabetes patients and all controls, using the modified Toronto Clinical Neuropathy scale (mTCNs, see below) [19] and a neurothesiometer (Scientific Laboratory Supplies, Nottingham, UK). For the present study, peripheral polyneuropathy was considered to be present using a 2.5 percentile cut-off point for abnormality using data from the matched healthy controls of the present study, when either mTCNs score was >5 points or the vibration perception threshold was >18.4 V.

Assessment of subjective sleep characteristics

Pittsburgh Sleep Quality Index The validated PSQI is a 19-item self-rated questionnaire for assessing subjective sleep quality over the previous month. These questions generate seven 'component' scores, each weighted equally from 0 to 3: subjective sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbances; use of sleep medication; and daytime dysfunction. The global PSQI score ranges from 0 to 21, with higher scores indicating worse sleep quality.

Epworth Sleepiness Scale The ESS is a validated eight-item questionnaire, focusing on the likelihood of falling asleep in several common situations encountered in daily life on a scale of 0 to 3. Scores range from 0 (the least sleepy) to 24 (the most sleepy). Scores equal to, or above, ten are interpreted as hypersomnolence [15].

Berlin Questionnaire The BQ consists of ten questions on risk factors for sleep apnoea, subdivided into three symptom categories: (1) snoring and apnoeas (six points); (2) wake-time sleepiness or fatigue (three points); and (3) the presence of obesity or hypertension (two points). If two or more categories are positive (categories 1 and 2: two or more points; category 3: one or more points), a person is at high risk of having sleep apnoea [16].

Evaluation of depression

Hospital Anxiety and Depression Scale The HADS consists of 14 items scoring anxiety and depression. Each item is measured on a four-point scale. Score for anxiety and depression subscale range from 0 to 21, and values of the total score range from 0 to 42. Higher scores indicate more severe anxiety or depression. A total score of 13 or more was considered to be increased [18]. This questionnaire was provided to the participants after the initial study day. Of the 99 patients, 87 (78.8%) and 80 of the 99 healthy controls (80.8%) returned the HADS questionnaire. The other questionnaires were completed by all participating type 1 diabetic patients and controls.

Assessment of peripheral polyneuropathy

Modified Toronto Clinical Neuropathy Scale The mTCNs consists of a brief easily administered semi-structured clinical interview and clinical sensory examination to assess symptoms and signs of diabetic sensorimotor polyneuropathy. The mTCNS rates individual symptoms (foot pain, numbness, tingling, weakness, imbalance, upper limb symptoms) as absent or present, and if present, grades them depending on interference with sense of well-being or activities of daily living. Symptoms without interference with sense of well-being or activities of daily living are graded as 1, those that interfere with sense of well-being, but not with activities of daily living as 2, and those that interfere with both as 3. The clinical sensory examination was performed unilaterally. In the case of previous trauma the unaffected leg was chosen, and otherwise the choice of the leg was random. Pinprick, temperature, light touch, vibration and position sense were graded as: (0) normal; (1) abnormal at the toes only; (2) between the toes and the ankle; or (3) or above the ankle [19]. For each of these modalities, reference stimuli were given to the dorsal site of one hand, after which testing was carried out on the sites described before, while individuals kept their eyes closed.

Neurothesiometer Before testing vibration perception threshold on the toes, participants were familiarised with vibration stimuli by applying these to the dorsum of one hand. Subsequently, vibration stimuli were applied bilaterally to the distal pulp of both toes. Individuals were instructed to indicate when vibration was first perceived. Vibration intensity was gradually increased until vibration was first detected by the patient or until a maximum output was reached. Testing was carried out with the individual's eyes closed. Testing was carried out twice on each toe, and a mean of both values was calculated in volts.

Statistical analysis

Data were analysed using PASW Statistics version 17.0.2 (SPSS, Chicago, IL, USA).

Continuous variables were described as mean±SEM; categorical variables were expressed as proportions. We used the paired *t* test and the McNemar test for differences in means and proportions for continuous and categorical

paired variables, respectively, and the two-tailed independent *t* test and the χ^2 test for unpaired data.

In patients with type 1 diabetes, logistic regression analysis was performed to examine the association of each sleep characteristic with poor glycaemic control (yes/no) adjusting for age, sex, BMI, use of alcohol (>1 glass/day, yes/no), and anxiety and depression scores according to the HADS.

To investigate variables for impaired sleep quality (PSQI>5) in the diabetic population, we fitted logistic regressions separately for all possible variables that could affect sleep quality: total exogenous insulin dose (units per kilogram per day), use of beta-blockers (yes/no), use of ACE inhibitors (yes/no), anxiety and depression score according to HADS, presence of hypertension (yes/no), nephropathy (yes/no), peripheral polyneuropathy (yes/no), macrovascular disease (yes/no), uncomfortable temperatures (yes/no), pain (yes/no), polyuria (yes/no), other sleep disturbances (e.g. metabolic dysregulation), habitual snoring (yes/no), high risk for OSA (yes/no), and RLS (yes/no). In these analyses, we adjusted for the confounders age, sex and BMI by including them as covariates. Subsequently, we performed multivariate logistic regression analysis—including age, sex, BMI, HbA_{1c}, duration of the diabetes and the risk factors that showed a *p* value of <0.2 in the preceding separate analyses.

Results

Clinical characteristics

We included 99 patients with type 1 diabetes and 99 healthy non-diabetic controls matched for sex (55 men, 44 women), age (43.9±1.3 vs 44.1±1.3 years) and BMI (24.5±0.3 vs 24.5±0.3 kg/m^2). The two groups did not differ with respect to current smoking status or use of alcohol or coffee. Clinical characteristics are summarised in Table 1.

Patients with type 1 diabetes used more frequently ACE inhibitors, calcium antagonists, statins, angiotensin II receptor antagonists and anti-platelet agents. According to the HADS, both anxiety (5.0±0.4 vs 3.7±0.3, p=0.004) and depression scores (3.3±0.4 vs 1.6±0.2, p=0.001) were significantly higher in the patients with type 1 diabetes. Thirteen patients (13.1%) had elevated scores for anxiety and depression (total HADS score 13 or more) vs six (6.1%) of the controls (p=0.267).The mean duration of the diabetes was 26.9±1.2 years. HbA_{1c} values were 7.8±0.1% (62±1.3 mmol/mol). Multiple daily insulin injections were used by 85 patients and the other 14 patients used continuous s.c. insulin infusion. The mean insulin dose was 0.70±0.0 Ukg^{-1} day^{-1}. Microvascular complications were present in 36 patients: 24 patients had retinopathy and 19 patients had nephropathy. The criteria for peripheral polyneuropathy were met by 45 patients compared with two of the matched healthy controls (p=0.000). Peripheral polyneuropathy was considered to be present, using a 2.5 percentile cut-off point for abnormality using data from the matched healthy controls of the present study, when either mTCNs score was >5 points or the vibration perception threshold was >18.4 V. Macrovascular complications were present in 15 patients.

Subjective sleep characteristics Self-reported mean duration of sleep in the PSQI did not differ between patients and controls (7.2±0.1 vs 7.1±0.1 h, p=0.372; Table 2). In addition, the proportion of short sleepers (<5 h) did not differ significantly between the two groups (1% vs 1%, p=1.00), and nor did the proportion of long sleepers (>9 h: 1% vs 1%, p=1.00). Although there were no significant differences in global PSQI scores between patients and controls, 35.4% of the patients had a total PSQI score >5, compared with only 19.2% of the controls, indicating a higher number of patients with poor sleep quality (p=0.021). In the individual domains of the PSQI questionnaire, patients more often reported sleep disturbances (p=0.001) and daytime dysfunction (p=0.031). The following sleep disturbances occurred more often in patients than in controls: polyuria (42.4% vs 24.2%, p=0.004), pain (8.1% vs 0%, p=0.008), uncomfortable temperatures (8.1% vs 1.0%, p=0.021) and habitual snoring (51% vs 34%, p=0.010).

The BQ indicated that more patients were at high risk for obstructive sleep apnoea (OSA) than controls (17.2 vs 5.1%, p=0.012). Despite the reduction in sleep quality and more sleep disorders, there were no significant differences in reported daytime sleepiness between the two groups. Daytime hypersomnolence affected 19.2% of the patients vs 11.1% of the controls (p=0.152).

Seventy-five patients answered the questions: 'Has your sleep been disturbed by hypoglycaemia in the past month? Has your sleep been disturbed by hyperglycaemia in the past month?' Forty-one patients indicated that their sleep was disturbed by hypoglycaemia in the past month: 34 patients indicated that their sleep was disturbed less than once per week, and seven patients indicated impaired sleep by hypoglycaemia one to two times per week. Disturbed sleep due to hyperglycaemia was reported by 28 patients with type 1 diabetes: 24 patients indicated disturbed sleep less than once per week, two patients one to two times per week, and two patients reported a disturbed sleep by hyperglycaemia more than three times per week.

Well-controlled vs moderate-to-poorly controlled patients

Type 1 diabetes patients were divided in two groups: well controlled (HbA_{1c}<7.5% [<58 mmol/mol], n=51) vs

Table 1 Clinical characteristics of the patients with type 1 diabetes and their non-diabetic matched controls

	Patients with type 1 diabetes (n=99)	Controls (n=99)	p value
Sex			
Male/female	55/44	55/44	1.000
Age (years)	43.9±1.3	44.1±1.3	0.472
BMI (kg/m^2)	24.5±0.3	24.5±0.3	0.986
BMI ≥30 kg/m^2	4 (4.0)	6 (6.1)	0.727
HbA_{1c}		NA	
%	7.8±0.1		
mmol/mol	62±1.3		
HbA_{1c} ≥ 7.5% (≥58 mmol/mol)	48 (48.5)		
Duration of diabetes (years)	26.9±1.2	NA	
Mean insulin dose (U kg^{-1} day^{-1})	0.7±0.0	NA	
Medications, n (%)			
Insulin		NA	
Continuous s.c. insulin infusion	14 (14.0)		
Insulin injections	86 (86.0)		
Beta-blockers	6 (6.1)	4 (4.0)	0.754
ACE inhibitors	29 (29.3)	5 (5.1)	0.000
Calcium antagonists	9 (9.1)	2 (2.0)	0.039
Statins	39 (39.4)	6 (6.1)	0.000
Oral glucose-lowering agents	1 (1.0)	0	1.000
Angiotensin II receptor antagonists	9 (9.1)	1 (1.0)	0.021
Diuretics	8 (8.1)	3 (3.0)	0.227
Oral contraceptives	7 (7.1)	8(8.1)	1.000
Anti-platelet agents	17 (17.2)	2 (2.0)	0.000
Proton pump inhibitors	6 (6.1)	2 (2.0)	0.289
Benzodiazepines	0	0	
Other	24 (24.2)	18 (18.2)	0.391
Diabetic complications, n (%)		NA	
Microvascular	36 (36.4)		
Retinopathy	24 (24.2)		
Laser treatment	18 (18.2)		
Nephropathy	19 (19.2)		
Macrovascular	15 (15.0)		
Peripheral polyneuropathy	45 (45.5)	2 (2.0)	0.000
mTCNs score	5.6±0.5	1.4±0.2	0.000
Neurothesiometer (V)	11.5±0.9	6.8±0.4	0.000
Hypertension, n (%)	24 (22.0)		
Current cigarette smokers, n (%)	18 (18.0)	11 (11.0)	0.210
Alcohol consumption ≥1 glass/day, n (%)	41 (41.4)	36 (36.4)	0.551
Coffee consumption ≥1 cup/day, n (%)	75 (75.8)	79(79.8)	0.307
HADS			
Anxiety score	5.0±0.4	3.7±0.3	0.004
Depression score	3.3±0.4	1.6±0.2	0.001
Total score	8.3±0.7	5.3±0.5	0.002
Score≥13	13 (13.1)	6 (6.1)	0.388

Data are mean±SEM for continuous variables and n (%) for categorical variables

NA, not applicable

moderate to poorly controlled (HbA_{1c}≥7.5% [≥58 mmol/mol], n=48). There were no significant differences in clinical characteristics between both groups. We found no significant differences between both groups in subjective sleep characteristics, i.e. self-reported sleep duration, sleep quality, daytime sleepiness, or the prevalence of

Table 2 Subjective sleep characteristics of the patients with type 1 diabetes vs matched non-diabetic controls

Sleep characteristic	Patients with type 1 diabetes (n=99)	Controls (n=99)	p value
Sleep duration			
Self-reported sleep duration (h)	7.2±0.1	7.1±0.1	0.372
Sleep quality			
PSQI			
Global score	4.6±0.3	4.0±0.2	0.079
PSQI >5, *n* (%)	36 (35.4)	20 (19.8)	0.021
Component score			
1. Subjective sleep quality	0.88±0.1	0.73±0.1	0.096
2. Sleep latency	0.68±0.1	0.74±0.1	0.598
3. Sleep duration	0.73±0.1	0.77±0.1	0.781
4. Sleep efficiency	0.31±0.1	0.22±0.1	0.307
5. Sleep disturbances	1.12±0.0	0.92±0.0	0.002
6. Sleeping medication	0.13±0.0	0.06±0.0	0.239
7. Daytime dysfunction	0.75±0.1	0.52±0.1	0.031
Daytime sleepiness			
ESS			
Total score	5.9±0.4	5.1±0.4	0.192
Score≥10, *n* (%)	19 (19.2)	11 (11.1)	0.152
Sleep disorders, *n* (%)			
BQ			
Habitual snoring	51 (51.0)	34 (34.0)	0.010
High-risk OSA	17 (17.2)	5 (5.1)	0.012
RLS	9 (9.3)	10 (10.1)	1.000

Data are mean±SEM for continuous variables and *n* (%) for categorical variables

sleep disorders (data not shown). Logistic regression analysis was performed to assess the association between self-reported sleep characteristics and high HbA_{1c} values (≥7.5% [≥58 mmol/mol]). There were no significant associations between individual sleep characteristics and impaired glycaemic control (Table 3).

Assessment of risk factors of impaired sleep quality (PSQI>5) in patients with type 1 diabetes

Logistic regression analyses for all possible variables that could affect sleep quality in patients with type 1 diabetes showed significant associations between impaired sleep quality and the presence of peripheral polyneuropathy (OR 2.98, 95% CI 1.05–8.46, p=0.040), habitual snoring (OR 4.19, 95% CI 1.47–11.97, p=0.007), uncomfortable temperatures (OR 7.89, 95% CI 1.31–47.31, p=0.024), other sleep disturbances, e.g. metabolic dysregulation (OR 9.52, 95% CI 1.03–88.17, p=0.047), HADS anxiety score (OR 1.20, 95% CI 1.02–1.40, p=0.026), and HADS depression score (OR 1.30, 95% CI 1.07–1.58, p=0.009; Table 4).

Multivariate logistic regression, including age, sex, BMI, HbA_{1c}, duration of diabetes and the risk factors, that showed a p value <0.2 in the preceding separate analyses confirmed that habitual snoring (OR 9.95, 95% CI 1.76–

Table 3 Results of logistic regression analysis of the association between sleep characteristics and impaired glucoregulation in 99 patients with type 1 diabetes

Sleep characteristic	HbA_{1c} ≥7.5% (≥58 mmol/mol)	
	OR (95% CI)	p value
Sleep duration[a]		
Self-reported sleep duration (h)	0.77 (0.48–1.24)	0.287
Sleep quality[a]		
PSQI		
Global PSQI score	1.06 (0.89–1.27)	0.532
PSQI >5	1.31 (0.47–3.63)	0.602
Daytime sleepiness[a]		
ESS		
Total ESS-score	1.04 (0.92–1.18)	0.521
ESS≥10	2.82 (0.84–9.42)	0.093
Sleep disorders		
BQ		
Habitual snoring	1.24 (0.51–3.01)	0.639
High-risk OSA	0.50 (0.15–1.59)	0.238
RLS	2.59 (0.59–11.41)	0.209

Each sleep characteristic was adjusted for age, sex, BMI and alcohol consumption (>1 glass/day)

[a]Also adjusted for HADS

Table 4 Results of logistic regression: possible risk factors for impaired sleep quality (PSQI >5) in 99 patients with type 1 diabetes

Characteristic	Poor sleep quality (PSQI >5)			
	Minimally adjusted model (adjusted for age, sex and BMI)		Maximally adjusted model	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Clinical characteristics				
Use of medication				
Total insulin dose (U kg^{-1} day^{-1})	1.32 (0.21–8.31)	0.768	NI	
Use of beta-blockers	1.00 (0.17–5.92)	0.996	NI	
Use of ACE inhibitors	0.42 (0.14–1.25)	0.118	0.85 (0.14–5.11)	0.859
Anxiety and depressive symptoms				
HADS anxiety score	1.20 (1.02–1.40)	0.026	0.91 (0.66–1.26)	0.572
HADS depression score	1.30 (1.07–1.58)	0.009	1.42 (1.00–2.02)	0.048
Diabetic complications				
Hypertension	0.41 (0.13–1.31)	0.133	0.38 (0.06–2.32)	0.292
Presence of nephropathy	0.88 (0.29–2.68)	0.828	NI	
Macrovascular disease	0.78 (0.21–2.92)	0.707	NI	
Presence of peripheral neuropathy	3.0 (1.05–8.46)	0.040	7.45 (1.08–51.20)	0.041
Sleep disturbances				
Uncomfortable temperatures	7.89 (1.31–47.31)	0.024	4.30 (0.27–69.45)	
Presence of pain	3.38 (0.72–15.84)	0.122	6.50 (0.50–84.43)	0.152
Polyuria	1.49 (0.20–3.97)	0.405	NI	
Other sleep disturbances, (e.g. metabolic dysregulation)	9.52 (1.03–88.17)	0.047	27.78 (1.11–697.48)	0.043
Sleep disorders				
Habitual snoring	4.20 (1.47–11.97)	0.007	9.95 (1.76–56.14)	0.009
High-risk OSA	1.27 (0.40–4.05)	0.682	NI	
RLS	0.89 (0.20–3.97)	0.883	NI	

NI, not included in final model because $p>0.2$

56.14, $p=0.009$), HADS depression score (OR 1.42, 95% CI 1.00–2.02, $p=0.048$), presence of peripheral polyneuropathy (OR 7.45, 95% CI 1.08–51.20, $p=0.041$) and other sleep disturbances (e.g. metabolic dysregulation [OR 27.78, 95% CI 1.11–697.48, $p=0.043$]) were still independent risk factors for poor sleep in the type 1 diabetes patients. Peripheral polyneuropathy, clinically assessed according to strict criteria, was an independent risk factor for impaired sleep, even after adjusting for 'pain' and 'uncomfortable temperatures'.

Discussion

The aim of this study was to assess subjective sleep characteristics in adult patients with long-standing type 1 diabetes, and to relate sleep variables to HbA_{1c} values. Although sleep duration did not differ between patients and controls, more patients had poor sleep quality compared with non-diabetic, age-, sex- and BMI-matched controls. Patients with type 1 diabetes reported more sleep disturbances and daytime dysfunction. A higher proportion of the patients with type 1 diabetes were at increased risk for OSA. There was no association between subjective sleep characteristics and impaired glucoregulation. These observations indicate that type 1 diabetes is associated with an increased prevalence of disturbed subjective sleep characteristics, which do not relate to glucoregulation.

Previous studies on the relation between diabetes and sleep characteristics mainly focussed on patients with type 2 diabetes [1, 2]. Only a few studies have assessed sleep characteristics in patients with type 1 diabetes [9–12]. Those studies investigated relatively few individuals and children [10–12] with type 1 diabetes. The present study extends those observations in showing that in a large group of adult patients with a long history of type 1 diabetes subjective sleep characteristics are impaired, compared with a carefully matched control group, controlling for potential confounding factors such as age, sex and BMI.

This decrease in sleep quality and increased prevalence of sleep disturbances in patients with long-standing type 1 diabetes may have important implications, as previous studies showed that reduction of sleep duration and/or

decreased sleep quality impair glucose tolerance and reduce insulin sensitivity in healthy controls [6–8]. Sleep disturbances might have a similar negative effect on glucose metabolism in patients with type 1 diabetes, resulting in worse diabetic control. However, this presumed relationship between sleep disturbances and impaired glucose metabolism, assessed by HbA_{1c} values, was not detectable in the current study. Nonetheless, it is still possible that disturbed sleep characteristics influence glucose metabolism in these patients. However, the effects of impaired sleep characteristics may not simply be reflected in HbA_{1c} values because intensive glucose control and frequent, appropriate adjustments of insulin doses in patients at risk might have obtunded the effects of impaired sleep characteristics on glucoregulation.

Various aspects of diabetes could be linked to disturbed sleep quality, including physical complications of the disease, psychological factors, metabolic fluctuations and high prevalence of sleep disorders. In the patients with type 1 diabetes in our study, disturbed sleep quality was independently associated with habitual snoring, higher depression scores according to the HADS questionnaire, presence of polyneuropathy and other sleep disturbances, mainly by hypoglycaemia.

Previous studies showed a high prevalence of depression in diabetes [20] and chronic pain conditions [21]. Although we excluded patients with a known depression, use of psychotropic drugs, and co-morbid disorders (other than neuropathy) associated with pain, in our study higher depression scores were independently associated with impaired sleep quality.

Many patients with type 1 diabetes in our study used ACE inhibitors, statins and/or beta-blockers, which might interfere with sleep characteristics. The effects of beta-blockers on sleep are not equivocal. A previous study showed that the use of beta-blockers could positively or negatively affect sleep [22]. A case report by Cicolin et al. suggested that ACE inhibitors may contribute to OSA by inducing upper airway inflammation [23]. Therefore, we have considered that the use of beta-blockers and/or ACE inhibitors might affect sleep quality in patients with type 1 diabetes. However, in univariate logistic regression analysis we did not find an association between the use of beta-blockers or ACE inhibitors and impaired sleep quality. In univariate logistic regression analysis there was an association between the use of ACE inhibitors and high risk of OSA. However, this association was no longer significant after correction for the confounders age, sex, BMI and hypertension. There are conflicting data on sleep disturbances in patients treated with statins. Some studies reported higher prevalence of sleep disturbances in patients treated with lipophilic statins than with pravastatin [24, 25] whereas other studies did not find an increased prevalence of sleep disturbances in patients treated with different statins compared with placebo [26, 27]. In the present study, there was no difference in the use of statins between patients with a poor sleep quality (PSQI>5) and patients with a good sleep quality (PSQI≤5). The use of statins was even higher in the group with good sleep quality. In accordance, in univariate analysis, use of statins was not associated with impaired sleep quality. Therefore, our conclusions are not likely to be merely explained by the use of medications in our patients.

The clinical assessment of peripheral polyneuropathy according to strict criteria in individuals with type 1 diabetes is a major strength of our study, as our study shows diabetic polyneuropathy was a major determinant of impaired sleep. Polyneuropathy contributes to impaired sleep via several potential mechanisms. First, neuropathic pain may lead to disturbed sleep [28]. Second, polyneuropathy can impair thermoregulation. It has been proposed that autonomic changes in skin temperature modulate the neuronal activity of the thermosensitive neurons in the pre-optic area/anterior hypothalamus, which, in turn, regulate vigilance and sleepiness [29]. This hypothesis is supported by a report showing that diabetic patients, even those without evidence of clinical neuropathy, show impaired thermoregulation during sleep [30].

The relatively high prevalence of type 1 diabetic patients with a high risk for OSA, according to the BQ, suggests the potential of a high burden of unrecognised OSA in people with type 1 diabetes. This is a relatively new finding, in accordance with a recent pilot study of Borel et al., which observed a prevalence of OSA of 40% in 37 non-obese adult patients with type 1 diabetes [31]. In accordance with our data, this observation is remarkable, as the BMI, which is a risk factor for OSA in the general population, of our patients with type 1 diabetes was matched to that of the healthy controls. Several studies in patients with type 2 diabetes have shown that OSA is associated with the presence of autonomic neuropathy [32, 33], which might also be involved in patients with type 1 diabetes. Unfortunately, our current study was not designed to elucidate underlying mechanisms of disturbed sleep, and we did not include assessments of autonomic neuropathy. Nonetheless, there was no association between poor glycaemic control (HbA_{1c}≥ 7.5%) and a ‘high’ risk for OSA in our study, despite the association between sleep-disordered breathing, glucose intolerance and insulin resistance in patients with type 2 diabetes [34, 35]. There was also no association between the occurrence of hypoglycaemia and the risk for OSA in our patients [36].

Sleep characteristics were assessed by validated questionnaires in the present study. The PSQI and ESS

have been developed to measure sleep quality and daytime sleepiness, respectively [14, 15], and reflect stable measures of sleep quality and sleepiness over the past year [37]. The PSQI has a diagnostic sensitivity of 89.6% and a specificity of 86.5% for identifying cases with poor sleep quality, using a cut-off score of 5. This questionnaire has been validated by polysomnographic measurements [38].The BQ is a screening tool widely used to differentiate between 'high-' and 'low-risk' groups for OSA. This risk grouping was useful in the prediction of respiratory disturbances in consecutive participants, who visited internists for any reason. For example, being in the 'high-risk' group defined by the BQ predicted more than five respiratory events per hour with a sensitivity of 86%, and a specificity of 77% [16]. In view of the current data, polysomnography is required to objectively assess the sleep quality and OSA in patients with type 1 diabetes mellitus at high risk for OSA according to the BQ.

The current cross-sectional study was designed to assess subjective sleep variables in patients with type 1 diabetes mellitus and, therefore, we cannot elucidate from the data which chain(s) of events lead from type 1 diabetes to disturbed sleep. In particular, the links between peripheral polyneuropathy and disturbed sleep and between type 1 diabetes and the risk of OSA are not fully clear. Another matter is whether disturbed sleep leads to further impairment of glucose metabolism, with the effect that sleep disturbances and glycaemic control can interact in a vicious circle. Additional studies with objective sleep measurements are warranted to assess these relations in more detail.

In conclusion, the present study demonstrated that adult patients with long-standing type 1 diabetes mellitus have altered self-reported sleep characteristics compared with sex-, age- and BMI-matched non-diabetic controls. Therefore, disturbed subjective sleep characteristics are part of the complex syndrome of long-standing type 1 diabetes mellitus.

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