groups [1]. However, gender differences regarding BP medication were confined to first-line antihypertensive use, and not overall antihypertensive drug use. This may suggest that women are more susceptible to the well-known adverse effects of ACEIs such as dry coughs, leading to the prescription of alternative antihypertensive agents.

One major strength of the present study is that it used data from a nationally representative sample of patients with T2D, thereby reflecting diabetes care in people with T2D living in communities. There are also limitations implicit in the population-based survey design of the present study. Severely ill persons are likely to be missed. Persons 80 years of age and older were not included in the study, as they are hard to reach and likely to be underrepresented in population surveys. In addition, the absolute number of persons with T2D was rather small compared to studies conducted in the primary care setting or based on diabetes registries.

In conclusion, the results of this nationwide population-based survey of adults aged 40–79 years with T2D in Germany indicate the presence of gender differences in cardiovascular profiles and persistent gender differences in CVD prevention, despite the introduction of disease management programmes for diabetes patients. In addition, gender differences in CVD risk need further elucidation to provide a sound evidence base for future guideline recommendations and diabetes care monitoring.

Contribution statement

Y.D. conceptualized the study, performed the statistical analyses and drafted the manuscript. J.B. supported the statistical analyses, reviewed and edited the manuscript, and contributed to the discussion of results. R.P., H.N. and C.H. reviewed and edited the manuscript, and contributed to the discussion of results. C.S.-N. conceptualized and supervised the study, and substantially contributed to the writing of the manuscript. Y.D. as the guarantor takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

All authors read and approved the final version of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

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Association of sleep apnoea syndrome and autonomic neuropathy in type 1 diabetes

Introduction

Obstructive sleep apnoea (OSA) is frequently observed in patients with type 2 diabetes (T2D), primarily because of the high prevalence of obesity. OSA is an independent risk factor for cardiovascular morbidity and mortality that also increases the risk of hypertension, stroke, acute coronary syndrome and arrhythmias. Also, OSA contributes to increased insulin resistance and glucose intolerance. A recent meta-analysis documented a high prevalence of sleep-disordered breathing in patients with type 1 diabetes (T1D) [1], while other studies have also examined the association between T1D and OSA [2–4]. Manin et al. [2] found an OSA prevalence [apnoea–hypopnoea index (AHI) $>$ 10/h] of 46% in 67 T1D patients using polysomnography, with severe OSA (AHI $\geq$ 30/h) detected in 19% of these patients, while Borel et al. [3] found sleep apnoea (defined as an AHI $\geq$ 15/h) in 40% of 37 subjects screened by nocturnal oximetry. Schober et al. [4] diagnosed OSA in 10.3% of 58 patients with T1D, who also had a high prevalence of autonomic neuropathy. However, the underlying mechanisms of OSA in T1D are currently poorly understood.

As sweat glands are innervated by autonomic C fibres, quantitative assessment of the sweat response has been proposed

as a method for evaluating autonomic neuropathy. Thus, the aim of the present study was to investigate the potential association between OSA and cardiac autonomic neuropathy (CAN) through quantitative assessment of sweat function in unselected patients with T1D treated with either multiple insulin injections or insulin pumps.

Materials and methods

Patients with T1D were recruited from the University Hospital of Strasbourg and the Hospitals of Mulhouse and of Saverne (Alsace, France). The study was approved by the medical ethics committee of Strasbourg University. Prior to participation, the investigator informed all subjects of what the study was about, after which they gave their informed consent. Patients were included if their age was > 18 years, they had T1D and their C-peptide levels were < 0.1 ng/L. Participants were excluded if they had T2D, endocrine disorders, psychiatric disorders, neuromuscular diseases, morphological maxillofacial or upper-airways abnormalities, or had been previously diagnosed with a sleep disorder or had a history of treatment with continuous positive airway pressure (CPAP).

A total of 50 consecutive patients were included and studied using ventilator polygraphy, followed by polysomnography (PSG) if the polygraphy was inconclusive for OSA. Nocturnal respiratory polygraphy, using an Embletta Gold testing device (Embla, Broomfield, CO, USA), was performed to measure nasal–oral airflow (nasal pressure cannula with oral thermistor), and chest and abdominal wall motion, using respiratory inductive plethysmography transducers, as well as arterial oxygen saturation with an oximeter, heart rate and body position. Standard nocturnal PSG (CID 102; Cidelec, Angers, France) was performed by recording the following: electroencephalography (EEG); electrooculography; chin electromyography; arterial oxygen saturation (SaO_2, by finger oximetry); nasal–oral oral airflow; suprasternal notch (by microphone); electrocardiography (ECG); chest and abdominal wall motion (piezoelectric electrodes); bilateral tibialis electromyography; and body position.

Respiratory events were scored using American Academy of Sleep Medicine (AASM) criteria. For both PSG and polygraphy, the AHI and 3% oxygen desaturation index (ODI) were defined by the number of desaturation events/h of measurement. A threshold of 10/h was chosen as the indicator for OSA confirmation, and mild-to-moderate OSA was indicated by an AHI > 10/h but < 30/h, with severe OSA defined as an AHI ≥ 30/h.

Autonomic neuropathy was evaluated by measuring sweat gland dysfunction using Sudoscan (Impeto Medical, Paris, France) [5]. Patients were asked to place their hands and feet on large electrodes for 2 min, during which time a voltage was applied with the direct current alternating between anode and cathode. The electric current stimulates the sympathetic sudomotor fibres innervating the sweat glands, which release NaCl. Cl^- is extracted by anode, and the flow of chloride-dependent current is measured and expressed as electrochemical skin conductance (ESC) for hands and feet. The CAN risk score was calculated from the ESC, body mass index (BMI) score and patient's age.

Data were analysed using SAS version 9.4 software (SAS Institute, Cary, NC, USA), and presented as medians and interquartile range [IQR] for continuous variables, and as frequencies for categorical variables. The study population was split into two groups, according to the presence or absence of OSA. Quantitative variables were compared between groups using the Mann-Whitney *U* test, as the data were not normally distributed. Proportions were compared using the Chi-square test or Fisher's exact test where appropriate. Spearman's correlation was estimated between CAN risk scores as well as AHI and ODI scores. To evaluate the risk of having OSA or an abnormal ODI according to CAN risk scores in the two groups (< 30% as the reference group), a multivariable logistic regression model was estimated. The regression model was checked to rule out the effects of collinearity and influential cases. The results were ultimately reported as odds ratios (ORs), with corresponding 95% confidence intervals (CIs). A *P*-value for trend was estimated by introducing the CAN risk score as a continuous variable to the model. A two-tailed *P*-value < 0.05 was considered statistically significant.

Results

In the present study, 52% of the total population was male, aged 51 [IQR 20] years, with a BMI of 25 [IQR 6] kg/m^2. The mean duration of diabetes at entry was 29 [IQR 24] years, with an HbA_{1c} of 8 [IQR 2] %. Fourteen subjects (28%) presented with sleep apnoea syndromes, with 13 (26%) of them exhibiting moderate OSA and one exhibiting severe OSA.

Demographic and clinical data according to the presence and absence of OSA are presented in Table 1. Patients with OSA had higher BMI scores, longer diabetes duration and higher rates of coronary heart disease. While HbA_{1c} did not differ between the two groups, patients with higher CAN risk scores (> 30%) had higher AHI (10.5 [10.6] vs. 2.4 [4.3]/h; *P* = 0.020) and higher ODI (11.4 [11.5] vs. 3.7 [5.1]; *P* = 0.016) scores. Of the 13 patients with CAN risk scores > 30%, seven (54%) had OSA, whereas seven of the 37 patients without CAN risk scores > 30% had OSA (19%; *P* = 0.03).

For the entire study population, a positive correlation was found between AHI during sleep and CAN risk score (Fig. 1). This

Table 1
Characteristics of the study participants according to the presence (OSA+) and absence (OSA−) of obstructive sleep apnoea (OSA).

	OSA− (*n* = 36)	OSA+ (*n* = 14)	*P*[a]
Age (years)	46.5 [16.0]	53 [16.8]	0.1096
Male gender	16 (44.4)	10 (71.4)	0.0864
Body mass index (kg/m^2)	24.4 [6.5]	28.2 [5.6]	**0.0232**
Overweight[b]	16 (44)	4 (28)	**0.0056**
Obese[c]	1 (3)	5 (36)	**0.0056**
Diabetes duration (years)	26.0 [22.0]	40.0 [12.0]	**0.0384**
HbA_{1c} (%)	7.9 [1.6]	7.4 [1.2]	0.2649
Implantable pump	1 (2.8)	1 (7.1)	0.3349
Subcutaneous pump	28 (77.8)	8 (57.1)	0.3349
Coronary heart disease	4 (11.1)	5 (35.7)	**0.0420**
Peripheral vascular disease	2 (5.6)	2 (14.3)	0.3069
Carotid stenosis	2 (5.6)	1 (7.1)	0.8319
Cerebrovascular disease	1 (2.8)	1 (7.1)	0.4794
Nephropathy	10 (27.8)	6 (42.9)	0.3047
Retinopathy	16 (44.4)	7 (50.0)	0.7234
Hypertension	15 (41.7)	8 (57.1)	0.3242
Dyslipidaemia	19 (52.8)	8 (57.1)	0.781
Tobacco-smoking	13 (36.1)	3 (21.4)	0.3176
Abnormal reflexes	8 (22.2)	6 (42.9)	0.1445
Abnormal monofilament test	7 (19.4)	5 (35.7)	0.2265
Abnormal diapason test	6 (16.7)	6 (42.9)	0.0515
Orthostatic hypotension	4 (11.1)	0 (0)	0.1935
Diarrhoea	3 (8.3)	1 (7.1)	0.8892
Abnormal neurological examination	11 (30.6)	7 (50.0)	0.1984
Apnoea–hypopnoea index (*n*/h)	1.3 [2.8]	18 [13.5]	< **0.0001**
Oxygen desaturation index	3.4 [4.0]	15.6 [12.4]	< **0.0001**
Cardiac autonomic neuropathy risk score (%)	17.0 [10.0]	30.5 [18.0]	**0.0012**

Data are expressed as *n* (%) for categorical variables and as medians [interquartile ranges] for continuous variables.
[a] By Chi-square or Mann-Whitney *U* test where appropriate; significant values are in bold.
[b] Body mass index (BMI) 25–30 kg/m^2.
[c] BMI ≥ 30 kg/m^2.

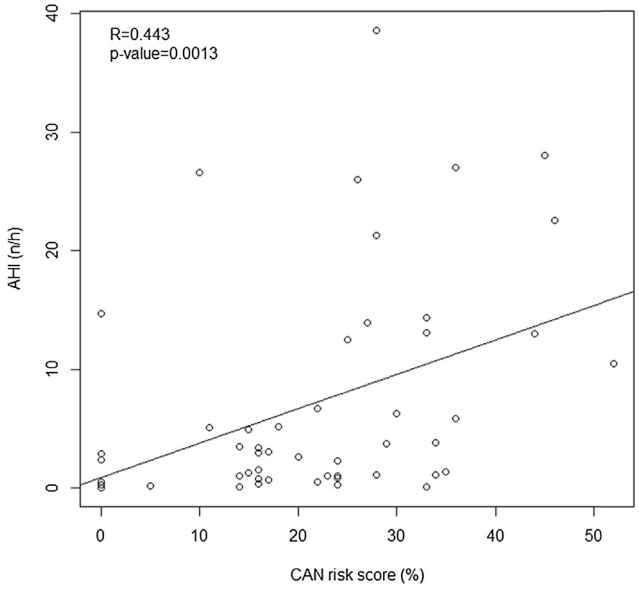

Fig. 1. Graph showing the positive correlation between apnoea–hypopnoea index (AHI) during sleep and cardiac autonomic neuropathy (CAN) risk scores.

association remained significant even after multivariate analysis adjusted for age, BMI, duration of diabetes and HbA_{1c} level (OR: 2.8 [0.63–12.50]; $P = 0.04$). Similarly, a positive correlation was found between the ODI and CAN risk score ($r = 0.451$, $P = 0.0016$), with the association remaining significant after multivariate analysis adjusted for age, BMI, duration of diabetes and HbA_{1c} level (OR: 3.9 [0.74–20.20]; $P = 0.03$).

Discussion

The present study has confirmed the high frequency of OSA in patients with T1D, and the even higher frequency of OSA in patients with a CAN risk score > 30%. In addition, our study has found a correlation between CAN risk score and AHI, and a positive association with the ODI, which remained significant after adjusting for variables.

Similar to previous reports, the present study found that the correlation between the presence of obesity and BMI was only slightly stronger in T1D patients with OSA. This suggests that factors other than obesity may play a role in the pathogenesis of OSA. However, a significant relationship was also demonstrated between neuropathy and the occurrence of OSA in both T1D and T2D patients.

Previous studies of only small patient cohorts found a greater incidence of sleep apnoea in those with diabetic autonomic neuropathy (DAN). Catterall et al. [6] found no differences in apnoea index (AI) between diabetics with and without DAN, whereas Neumann et al. [7] reported a significant correlation between the number of oxygen desaturations during sleep and severity of DAN. Ficker et al. [8] studied two groups of diabetes patients: 23 with DAN; and 25 without DAN. Six patients with DAN (26%) were found to have OSA, but none of those without DAN met the diagnostic criteria. When patients with OSA were compared with those without OSA, no differences were found in age, gender, BMI, or diabetes type or duration. Bottini et al. [9] assessed the occurrence and nature of sleep-disordered breathing in 26 adult non-obese diabetics. In contrast to controls and patients without DAN, who showed no sleep-disordered breathing, five patients with DAN had an AHI > 10/h and four patients with DAN had an AI > 5/h. No periodic breathing or central sleep apnoeas were found in DAN patients with orthostatic hypotension, although all had enhanced central chemoresponsiveness to CO_2. In addition, the adult non-obese diabetics with autonomic neuropathy had an OSA/hypopnoea frequency of 30%.

More recently, Janovsky et al. [10] evaluated 20 non-obese patients using PSG for OSA assessment and cardiac autonomic reflex tests (CARTs) for CAN assessment (at least two positive tests). Results showed that patients with CAN had significantly higher prevalences of sleep apnoea compared with other groups: 67% in patients with CAN vs. 23% in patients without CAN and 4.5% in controls (with CAN vs. controls: $P = 0.006$; with CAN vs. without CAN: $P = 0.02$). In addition, the prevalence of OSA was higher in diabetes patients with CAN. The CAN risk score used in this study was also evaluated in several clinical studies. Selvarajah et al. [5] used receiver operating characteristic (ROC) curve analysis to show that the CAN risk score had an area under the curve (AUC) of 0.75, and a sensitivity of 65% and specificity of 80% to detect CAN when evaluated by at least one positive CART in patients with T1D.

The present study had several limitations. First, as the study had a cross-sectional design, no assumptions of causality could be made. Second, although the study involved a larger sample size than in previous studies, the number of participants was limited to 50, thereby introducing some uncertainty into the statistical analysis, such as large CIs for logistic regression analysis. Third, CARTs were not used to confirm CAN as assessed by CAN risk scores and, finally, the study did not include an analysis of glycaemic control, which may play a role in OSA.

Conversely, the main strength of our study was that it established an AHI threshold of > 10/h, which is more specific than the classic value of > 5/h and, thus, was able to limit the finding of false positives for OSA.

In conclusion, CAN is associated with a high frequency of OSA in T1D patients. Future research conducted with larger sample sizes and further explorations of autonomous neuropathy are now needed to expand the current findings.

Author contributions

L.M. wrote the manuscript and researched data; M.M., C.C., P.A., A.E.P., E.W., C.I., T.B., R.K. and B.R.-P. researched data and reviewed the manuscript; L.K. researched data, contributed to discussion and reviewed the manuscript.

Guarantor's statement

Dr Laurent Meyer is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Disclosure of interest

The authors declare that they have no competing interest.

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Association of handgrip strength with B-type natriuretic peptide levels and cardiovascular events in patients with type 2 diabetes

B-type natriuretic peptide (BNP) is a useful predictor of cardiovascular (CV) events and death in patients with heart failure [1,2]. BNP is also a powerful predictive marker of CV events beyond heart failure and death in patients with type 2 diabetes (T2D) [3]. Previous studies have shown that, in healthy individuals, exercise induces BNP secretion, which may have cytoprotective effects on the heart [4]. In addition, recent studies have shown that natriuretic peptides, including BNP, play a role in lipid oxidation in fat tissue and in enhancing oxidative capacity in skeletal muscle [4]. Handgrip exercise increases BNP levels by 30% in healthy men [5], while moderate-intensity walking increases BNP levels in patients with cardiovascular disease (CVD), but not in healthy people or in patients with CV risk factors [6]. In contrast, low-intensity daily physical activity is associated with an increase in BNP levels in patients with T2D [7]. However, the association between exercise and BNP levels may change depending on the disease/condition or level of physical fitness. Yamashita et al. [8] showed that muscle mass measured by cross-sectional area of thigh muscle was negatively associated with plasma BNP levels in healthy people. However, no researcher has investigated the association of handgrip strength, a simple and useful method for evaluating muscle strength, with BNP levels and CV events in patients with T2D. Thus, the present study aimed to examine those associations in such patients.

This retrospective cohort study was conducted in T2D patients treated at the National Center for Global Health and Medicine, Kohnodai Hospital. Between April 2013 and December 2015, outpatients whose handgrip strength and plasma BNP levels were measured at the same time were included. Patients were instructed to consume a calorie-restricted diet of 25–30 kcal/kg (ideal body weight)/day as dietary therapy for diabetes by certified nutritional educators, and to continue the diet throughout the study period. CV events included stroke and non-fatal coronary heart disease.

The study protocol was approved by the Medical Ethics Committee of the National Center for Global Health and Medicine (Reference No. NCGM-G-002052), and the study was performed in accordance with the Declaration of Helsinki.

Height was measured using a rigid stadiometer (Tsutsumi Co., Ltd., Tokyo, Japan). Weight was measured using calibrated scales (AD-6107NW; A&D Company Limited, Tokyo, Japan). Body mass index (BMI) was calculated as body weight in kg divided by height in m^2. Blood pressure was measured in a sitting position using an automatic sphygmomanometer (HBP-9020; Omron Healthcare Co., Ltd., Kyoto, Japan).

Handgrip strength was measured in each hand using a Smedley analogue hand dynamometer (No. 04125; MIS, Tokyo, Japan) in standing position. Measurements were taken of the dominant hand first. Subjects performed a maximum of two attempts for each hand with an approximately 1-min rest period in between, and their average handgrip strength was calculated in kg. Patients were also asked about their regular exercise habits, and their daily exercise times were calculated using a questionnaire.

Blood samples were drawn in the morning from an antecubital vein. Plasma glucose, haemoglobin A_{1c} (HbA_{1c}) and BNP levels were measured. Plasma BNP levels were measured using a specific immunoradiometric assay for human BNP (Architect BNP-JP®, Abbott Japan Co., Ltd., Tokyo, Japan). Estimated glomerular filtration rate (eGFR) was calculated using the revised equation adjusted for the Japanese population [9].

Statistical analyses were performed using SPSS version 24 software (IBM Corp., Armonk, NY, USA). All values were expressed as means ± standard deviation (SD). Multiple regression analysis, adjusted for age, gender, BMI, exercise time, systolic blood

Table 1
Clinical characteristics of subjects with type 2 diabetes.

	Mean ± SD
Demographic data	
Age (years)	64.7 (14.1)
Gender (males/females)	253/183[a]
Exercise time (min/day)	16.1 (9.1)
Duration of diabetes (years)	11.8 (11.6)
Anthropometric data	
Height (cm)	160.4 (9.9)
Weight (kg)	66 (17.5)
Body mass index (kg/m^2)	25.4 (5.8)
Handgrip strength (kg)	23.4 (9.9)
Physiological and biochemical data	
Systolic blood pressure (mmHg)	135.5 (21.9)
Diastolic blood pressure (mmHg)	75.4 (14.9)
Plasma glucose (mg/dL)	179.5 (73.9)
HbA_{1c} (%)	8.2 (2)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	72.7 (27.4)
Plasma B-type natriuretic peptide	44.9 (105.9)

[a] *n*/*n*.