Check for updates

Received: 11 September 2020 | Revised: 13 February 2021 | Accepted: 19 February 2021

DOI: 10.1111/jsr.13331

REGULAR RESEARCH PAPER

Journal of Sleep Research

Positive airway pressure (PAP) treatment reduces glycated hemoglobin (HbA1c) levels in obstructive sleep apnea patients with concomitant weight loss: Longitudinal data from the ESADA

Mehmet Sezai Tasbakan[1] | Ludger Grote[2] | Jan Hedner[2] | John Arthur Kvamme[3] | Johan Verbraecken[4] | Walter T. McNicholas[5] | Gabriel Roisman[6] | Ruzena Tkacova[7] | Maria R. Bonsignore[8] | Tarja Saaresranta[9] | Paschalis Steiropoulos[10] | Oreste Marrone[11] | Ozen K. Basoglu[1] | ESADA Collaborators

[1]Department of Chest Diseases, Ege University Faculty of Medicine, Izmir, Turkey

[2]Sleep Disorders Center, Center for Sleep and Wake Disorders, Sahlgrenska University Hospital, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden

[3]Sleep Laboratory, ENT Department, Førde Central Hospital, Førde, Norway

[4]Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium

[5]Department of Respiratory Medicine, School of Medicine, St Vincent's Hospital Group, University College Dublin, Dublin, Ireland

[6]Sleep Disorders Centre, Hospital Antoine-Beclere, Clamart, France

[7]Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P.J. Safarik University, Kosice, Slovakia

[8]PROMISE Dept, University of Palermo, Palermo, Italy

[9]Division of Medicine, Department of Pulmonary Diseases, Department of Pulmonary Diseases and Clinical Allergology, Turku University Hospital and Sleep Research Centre, University of Turku, Turku, Finland

[10]Sleep Unit, Department of Pneumonology, Democritus University of Thrace, Alexandroupolis, Greece

[11]National Research Council, Istituto per la Ricerca e l'Innovazione Biomedica, Palermo, Italy

Correspondence
Mehmet Sezai Tasbakan, Department of Chest Disease, Faculty of Medicine, Ege University, Izmir, Turkey.
Email: sezai.tasbakan@ege.edu.tr; sezai72000@yahoo.com

Summary

Patients with obstructive sleep apnea (OSA) are at increased risk of developing metabolic disease such as diabetes. The effects of positive airway pressure on glycemic control are contradictory. We therefore evaluated the change in glycated hemoglobin (HbA1c) in a large cohort of OSA patients after long-term treatment with positive airway pressure. HbA1c levels were assessed in a subsample of the European Sleep Apnea Database [n=1608] at baseline and at long-term follow up with positive airway pressure therapy (mean 378.9±423.0 days). In a regression analysis, treatment response was controlled for important confounders.

Overall, HbA1c decreased from 5.98±1.01% to 5.93±0.98% (p=0.001). Patient subgroups with a more pronounced HbA1c response included patients with diabetes (−0.15±1.02, p=0.019), those with severe OSA baseline (−0.10±0.68, p=0.005), those with morbid obesity (−0.20±0.81, p<0.001). The strongest HbA1c reduction was observed in patients with a concomitant weight reduction >5 kilos (−0.38±0.99, p<0.001). In robust regression analysis, severe OSA (p=0.038) and morbid obesity (p=0.005) at baseline, and weight reduction >5 kilos (p<0.001) during follow up were

[Correction added on 31 August 2021, after first online publication: The collaborators group name and list of collaborators were previously missed from the published version and have been added]

 © 2021 European Sleep Research Society

independently associated with a reduction of HbA1c following PAP treatment. In contrast, PAP treatment alone without weight reduction was not associated with significant Hb1Ac reduction.

In conclusion, positive airway pressure therapy is associated with HbA1c reduction in patients with severe OSA, in morbidly obese patients. and most obviously in those with significant weight lost during the follow-up. Our study underlines the importance to combine positive airway pressure use with adjustments in lifestyle to substantially modify metabolic complications in OSA.

KEYWORDS

HbA1c, positive airway pressure therapy, sleep apnea

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by instability of the upper airways during sleep, resulting in a reduction of airflow, oxygen desaturation and sleep disruption. The prevalence of moderate-to-severe OSA is 23.4% in women and 49.7% in men (Heinzer et al., 2015). Using AASM 2012, it is estimated that 936 million adults aged 30–69 years (men and women) have mild to severe OSA globally (Benjafield et al., 2019). Cardio-metabolic disease such as systemic hypertension and diabetes mellitus (DM) are common in patients with OSA (Lattimore et al., 2003; Schlatzer et al., 2014). With regard to diabetes, there is evidence from a number of studies to suggest that 15%–30% of individuals with OSA have type 2 diabetes (T2D), and that OSA is an independent risk factor for this comorbidity (Pamidi & Tasali, 2012). A variety of mechanisms may explain the link between OSA and disturbed glucose metabolism or development of T2D. These include activation of the sympathetic nervous system by intermittent hypoxia and sleep fragmentation. Furthermore, direct effects of hypoxia on glucose metabolism and insulin sensitivity as well as increased release of cytokines contributing to insulin resistance have been reported in OSA (Chakhtoura & Azar, 2012).

Positive airway pressure (PAP) therapy is the gold-standard treatment for OSA. Although PAP can be a very successful therapy in terms of apnea reduction, the effects of such treatment on insulin sensitivity and glycaemic control in T2D are insufficiently clarified. In a meta-analysis of uncontrolled studies, PAP treatment was found to improve glucose metabolism both in diabetic and non-diabetic subjects. In contrast, a recent systematic review summarized nine sham-controlled studies investigating the effect of PAP on glucose metabolism. Five studies showed no effects on different markers of glycaemic health, and the remaining studies reported variable results. In conclusion, the controlled trials could not support the findings of the observational studies (Jullian-Desayes et al., 2015; Yang et al., 2013). On the other hand, these trials were hampered by short treatment duration and limited sample sizes.

In the setting of the large, prospective European Sleep Apnea Database (ESADA) cohort study, we aimed to assess the effects of PAP on glycaemic control. We hypothesized that PAP effects were more pronounced in patients with severe sleep apnea and comorbid obesity. For this purpose, we studied the PAP effects on glycated haemoglobin (HbA1c), a well-established parameter for glycaemic control during the past 3 months, in patients with different degrees of OSA and comorbidities.

2 | MATERIALS AND METHODS

The ESADA study is a pan-European, multicentre, prospective study, and the current analysis included data from 33 sleep clinics across 19 countries (Hedner et al., 2011). ESADA was established to investigate the role of OSA in driving cardiovascular and metabolic morbidity and mortality, with the goal of prospectively evaluating a large cohort of subjects with sleep-disordered breathing. ESADA uses a web-based collection platform to facilitate transfer of data from individual centres to the central database at the University of Gothenburg.

2.1 | Patients

Sleep apnea patients on current treatment with PAP, aged 18 years and above, with an assessment of HbA1c at baseline and during PAP follow-up, and with an enrollment date in the ESADA from March 2007 to December 2017 (n = 1,608). Patients referred for assessment at any of the participating centres were considered eligible, unless they were receiving treatment of previously diagnosed OSA, had ongoing substance abuse, or had a severe comorbidity with short life expectancy. At baseline, demographic, anthropometric and clinical variables, including measured body mass index (BMI), smoking history, comorbidities and medication usage, were recorded for each patient. The patients used PAP treatment for at least 3 months. The patients were considered to be diabetic if they had clinician-diagnosed diabetes in combination with anti-diabetic medication. Research ethics committee approval for the study was obtained at

13652869, 2021, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jsr.13331 by University Degli Studi Di Palermo, Wiley Online Library on [26/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

each of the participating centres. Oral and written informed consent was obtained from all participants.

2.2 | HbA1c measurement

Participating patients provided a venous blood sample for assessment of HbA1c levels measured according to Diabetes Control and Compliance Trial (DCCT)-accredited laboratories both at baseline and PAP treatment follow-up (Nathan et al., 2014). Both blood samples were analysed at the same laboratory, eliminating between-laboratory variability of HbA1c measurements.

2.3 | Sleep studies

A detailed description of the sleep study methodology in the ESADA has been published previously (Escourrou et al., 2015). Full polysomnography (PSG, n = 1,604) was performed according to local practice. All sleep data were manually edited according to protocol definitions. Polygraph (PG) recordings included a minimum of four recording channels (level 3 devices according to the American Academy of Sleep Medicine [AASM]) (ASDA, 1994), while PSG studies were performed and analysed according to AASM criteria. Scoring of sleep studies in ESADA was performed in accordance with AASM 2007 rules; the apnea–hypopnea index (AHI) and the oxyhaemoglobin desaturation index (oxygen desaturation criteria of 4%) were defined per hour of sleep for PSG and per hour of analysed time for PG recordings (Iber et al., 2007). The Epworth Sleepiness Scale (ESS) was used to assess subjective daytime sleepiness (Johns, 1991). Sleep study scoring in ESADA has been discussed in more detail elsewhere (Escourrou et al., 2015; Hedner et al., 2011).

2.4 | Treatment and follow-up procedure

The ESADA registry captures information on OSA treatment, and allows for specific clinical follow-up routines practiced at each study site. At the treatment follow-up visit, information on anthropometric assessments and the ESS score were collected. Details on the type of PAP device (e.g. auto-adjusting, continuous or bi-level), treatment start/stop time, mean administered pressure (mbar) and compliance (hours of use per day collected from machine time counter) were documented in PAP-treated patients.

2.5 | Description of the OSA alleviation calculation

Obstructive sleep apnea alleviation, a measure of overall OSA reduction by PAP therapy including PAP compliance in relation to habitual sleep time and residual AHI (Grote et al., 2000), was computed for 372 patients. The formula is as follows: (PAP compliance/subjective sleep − time) × [baseline AHI − (% PAP use) × (baseline AHI × (1 − AHI with PAP/baseline AHI))].

2.6 | Analysis of data

Statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM) and Stata 11. 0 (StataCorp, 2009; Stata Statistical Software: Release 11, College Station, TX: StataCorp LP). The primary end point was the change in HbA1c measured after at least 3 months of PAP treatment (Wilcoxon test, entire study population). In order to further explore the PAP treatment effects, we performed analysis of the HbA1c change by PAP according to gender, diabetes status, severity of OSA syndrome, BMI class and weight change class in follow-up. Student's t-test, Mann–Whitney U-test and one-way ANOVA were used in these analyses. Then, robust regression analysis was performed to determine the factors that have an independent effect on the HBA1c change. We included confounding variables found to be significant in the univariate analysis in the final model. Robust regression analysis (M estimation) was performed because the normal distribution assumptions were not met for the outcome variable (HbA1c change). Because the independent variables are categorical, these variables were included in the model as dummy variables.

3 | RESULTS

3.1 | Main analysis of change in HbA1c levels at follow-up

From March 2007 to December 2017, 22,851 subjects were enrolled in the ESADA database. A total of 5,079 of these patients were diagnosed with OSA and given PAP therapy. A total of 1,608 patients, 336 of them with treated diabetes, used a PAP device for more than 90 days (mean 378.9 ± 423.0 days) and had HbA1c measurements available for both baseline and follow-up (Figure 1). Demographic and clinical data of the total study population as well as diabetic and non-diabetic patients are given in Table 1. For the entire study group, a small HbA1c reduction was observed at PAP therapy follow-up (5.98 ± 1.01 versus 5.93 ± 0.98, p = .001).

3.2 | Change in HbA1c during long-term PAP treatment in subgroups of OSA patients

3.2.1 | Diabetic patients

Nearly all diabetic patients (295/336, 87.8%) used antidiabetic drugs (oral antidiabetic or insulin) at baseline. Factors influencing the HbA1c changes were evaluated separately for diabetic and non-diabetic patients (Table 2). In general, HbA1c reduction was more prominent in patients with diabetes compared with non-diabetes patients

13652869, 2021, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jsr.13331 by University Degli Studi Di Palermo, Wiley Online Library on [26/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

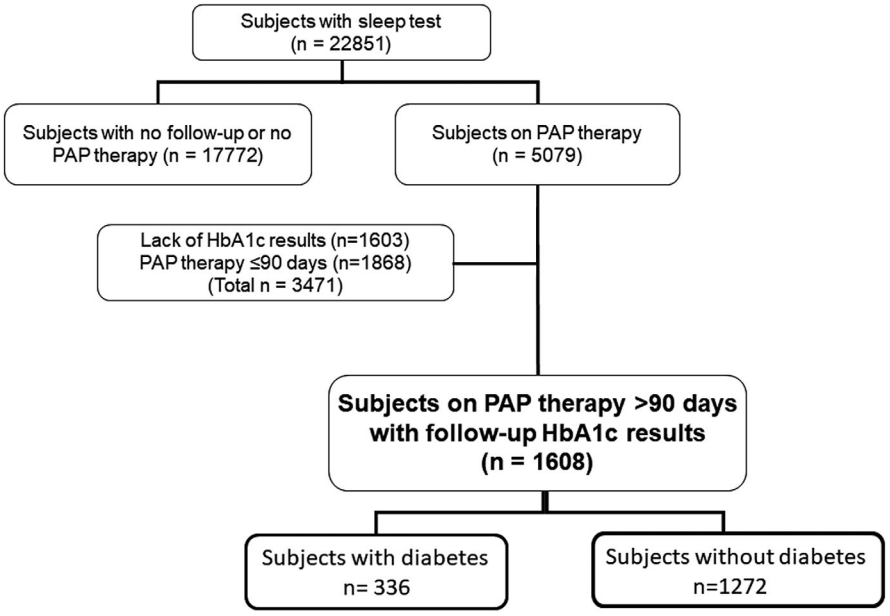

FIGURE 1 Study flow chart. PAP, positive airway pressure

TABLE 1 Characteristics of the study population

Parameter	Total (n = 1,608)	Diabetic OSA patients (n = 336)	Non-diabetic OSA patients (n = 1,272)	Between group comparisons (p-value)
Age (years)	53.9 ± 10.8	57.3 ± 9.1	53.0 ± 10.0	< .001
Male gender, *n* (%)	1,193 (74.2)	214 (63.7)	979 (77.0)	< .001
Current smoker, *n* (%)	371 (23.1)	69 (20.5)	302 (23.7)	.121
BMI (kg m^{-2})	32.8 ± 7.0	36.0 ± 7.7	31.9 ± 6.3	< .001
Comorbid diseases				
Systemic hypertension, *n* (%)	779 (48.4)	251 (74.7)	528 (41.7)	< .001
Coronary artery disease, *n* (%)	169 (10.5)	70 (20.8)	99 (7.8)	< .001
Hyperlipidaemia, *n* (%)	523 (32.5)	149 (44.3)	374 (29.5)	< .001
COPD, *n* (%)	75 (4.7)	22 (6.5)	53 (4.2)	.05
ESS score	10.1 ± 5.1	10.4 ± 5.2	10.1 ± 5.0	.355
AHI (events hr^{-1})	40.4 ± 24.5	43.2 ± 25.5	39.6 ± 24.2	< .018
Baseline HbA1c (%)	5.98 ± 1.01	7.14 ± 1.29	5.67 ± 0.63	< .001
Follow-up HbA1c (%)	5.93 ± 0.98	6.98 ± 1.36	5.65 ± 0.59	< .001
Mean PAP duration (days)	378.9 ± 423.0	298.2 ± 384.2	400.2 ± 430.3	< .001
Mean PAP compliance (hr)	5.3 ± 2.0	5.2 ± 2.1	5.3 ± 1.9	.258

AHI, apnea–hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESS, Epworth Sleepiness Scale; HbA1c, glycated haemoglobin; OSA, obstructive sleep apnea; PAP, positive airway pressure.

(−0.15 versus −0.03, $p = .036$). In patients with diabetes, significantly stronger HbA1c reduction was observed in those individuals with severe OSA (AHI ≥ 30 events hr^{-1}), morbid obesity and a weight reduction exceeding 5 kilos during follow-up (HbA1c change −0.24, −0.38 and −0.76, $p = .002$, $p < .001$ and $p < .001$, respectively).

3.2.2 | Gender

Diabetes was more prevalent in female than in male patients (29.5% versus 18.0%, $p < .001$), and baseline HbA1c levels were higher in female compared with male OSA patients (6.13 ± 1.11 versus 5.93 ± 0.97; $p = .003$, respectively). However, HbA1c was reduced to a comparable extent in both genders (−0.04 in males and −0.10 in females, $p < .001$, respectively, between-group difference $p = .116$).

3.2.3 | Sleep apnea severity

The change in HbA1c was more pronounced in patients with severe (AHI ≥ 30 events hr^{-1}) compared with those with mild OSA (AHI 5

13652869, 2021, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jsr.13331 by University Degli Studi Di Palermo, Wiley Online Library on [26/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 Change in HbA1c according to DM presence

	Patients with diabetes ($n = 336$)	Patients without diabetes ($n = 1,272$)	Within group difference pre-, post-treatment, diabetes patients (p value)	Within group difference pre-, post-treatment, non-diabetes patients (p value)	Between group difference (p value)
HbA1c (%) change	−0.15	−0.03	0.007	0.016	**0.036**
AHI classes					
5–15 events/hr	+0.11	+0.04			NS
15–30 events/hr	−0.08	−0.02	0.095	0.055	NS
≥30 events/hr	−0.24	−0.06			**0.002**
BMI classes					
<25 kg/m^2	+0.22	+0.06			**0.012**
25–35 kg/m^2	+0.06	−0.02	<0.001	0.001	NS
>35 kg/m^2	−0.38	−0.11			**<0.001**
Weight change					
>(+5) kg	+0.10	+0.05	**<0.001**	**<0.001**	NS
(+2)–(+5) kg	+0.19	+0.04			NS
(−2)–(+2) kg	−0.09	−0.00			NS
(−2)–(−5) kg	+0.05	−0.16			NS
<(−5) kg	−0.76	−0.24			**<0.001**

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure.

to < 15 events hr^{-1}) at baseline (−0.10 versus +0.05, respectively, $p < .005$; Figure 2; Table 3).

3.2.4 | Body weight

The HbA1c change was most prominent in morbidly obese patients (−0.20 ± 0.81, $p < .001$), while HbA1c increased slightly in normal weighted OSA patients (BMI < 25 kg m^{-2}; Figure 3). When subdivided into quintiles of observed weight change during the follow-up period, the largest HbA1c decrease was observed in patients with a concomitant weight loss of > 5 kg (−0.38 ± 0.99, $p < .001$; Figure 4). Conversely, weight increase was associated with a non-significant HbA1c increase despite ongoing PAP therapy (+0.06 ± 0.59, $p = .171$).

3.2.5 | Adherence and OSA alleviation with PAP treatment

Adherence with (hours of use per night) and duration of PAP therapy (3–12 months versus > 12 months, $n = 603$ and $n = 1,005$, respectively) were not associated with the degree of HbA1c reduction ($p = .917$ and $p = .978$, respectively). In patients with PAP adherence of ≥4 without weight reduction (n=995) Hb1Ac was unchanged whereas the combination of adequate PAP adherence and weight reduction ≥5 kg resulted in a significant Hb1Ac reduction (−0.28, n=280). In contrast, "OSA alleviation", which accounts for PAP adherence adjusted for habitual sleep time and efficacy of PAP treatment (residual AHI), was dose-dependently associated with the change in HbA1c (−0.31 ± 0.98 versus −0.04 ± 0.72 and −0.18 ± 0.51, $p = .034$ in > 50%, 0%–20% or 20%–50% of OSA alleviation, respectively; Figure 5; Table 3). In addition, weight loss was found to have an additional contribution to HbA1c reduction in the group with OSA alleviation greater than 50%. While the change in HbA1c was −0.31±0.98 in the group with OSA alleviation greater than 50%, HbA1c change was −1.04±−1.29 in those with additional weight lost >5 kg (p<0.001).

3.3 | Predictors of HbA1c decrease with PAP treatment

For the analyzes, the change in HbA1c levels after PAP treatment was accepted as the continuous dependent variable, while age, gender, PAP compliance parameters, diabetes diagnosis, OSA severity, obesity, and weight reduction classes were accepted as independent variables. Univariate analysis performed in the entire study population of 1,608 OSA patients demonstrated that diabetes diagnosis, OSA severity, obesity and weight reduction were significantly associated with HbA1c reductions (all $p < .05$). All significant variables in univariate analysis were included in the robust regression model and morbid obesity ($p = .005$), severe OSA ($p = .038$) and weight reduction > 5 kilos ($p < .001$) were found independently associated with HbA1c reduction (Table 4).

4 | DISCUSSION

In the largest prospective cohort study to date, we observed a dose–response relationship between OSA alleviation during long-term PAP therapy and improved glycaemic health. This association was small but clinically significant for the entire population. We identified a number of subgroups with more relevant HbA1c reductions: diabetic and non-diabetic OSA and patients with

13652869, 2021, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jsr.13331 by University Degli Studi Di Palermo, Wiley Online Library on [26/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

severe OSA, patients with morbid obesity at baseline. However, the most obvious HbA1c decrease was observed in those with significant weight lost (at least 5 kg) during the follow-up. The key message from our data is that PAP treatment may have a small beneficial effect on glycaemic health, but only the combination of PAP treatment with lifestyle changes results in a clinically meaningful impact on glycaemic health. Our study was performed in a multinational population of OSA patients across Europe, which increases the impact and generalizability of our findings.

4.1 | Sleep apnea and glycaemic health

Our data suggest a dose–response relationship between OSA severity at baseline and PAP effects on HbA1c levels. Indeed, the cross-sectional analysis of our ESADA cohort demonstrated a strong association of OSA severity with HbA1c levels in non-diabetic subjects (Kent et al., 2014). Subsequently, it was shown that OSA severity predicted an increased likelihood of concomitant T2DM and worse control of diabetes in patients with T2DM (Kent, Grote, & Ryan, 2014). The link between sleep apnea and the risk for diabetes is further evidenced by prospective data from population-based studies, including the Sleep Heart Health Study (Nagayoshi et al., 2016) and the Hypnolaus study (Heinzer et al., 2015).

4.2 | OSA treatment and glycaemic health

Malik et al. showed that 59% of 62 diabetic OSA patients improved glycaemic control, measured as HbA1c, after PAP treatment (Malik et al., 2017). In another controlled study, assessing the effect of 6-month PAP therapy on HbA1c in 26 patients with sub-optimally controlled diabetes and OSA, PAP significantly improved glycaemic control (Martínez-Cerón et al., 2016). In contrast to previous studies, long-term CPAP in addition to usual care in OSA patients with manifest cardiovascular diseases was not associated with improved glycaemic control in those with diabetes, or prevention of new diabetes diagnoses, compared with usual care alone (Loffler et al., 2020). However, this sub-analysis within the SAVE study included a less symptomatic subpopulation of OSA that may be significantly different from the group of studies included in the current ESADA cohort reflecting a reference patient cohort referred to tertiary sleep centres. In the present study, HbA1c decreased in patients with and without diabetes. As expected, more prominent reduction of HbA1c was observed in OSA patients with T2D. Moreover, in our study, severe OSA was observed more frequently in patients with diabetes, and the reduction of HbA1c was prominent in those patients with severe OSA. Collectively these findings suggest that OSA patients with elevated HbA1c may benefit particularly well from PAP therapy when compared with weight reduction. There are only limited data in the literature on this topic. In a meta-analysis of uncontrolled studies, PAP treatment was found to improve glucose metabolism both in diabetic and non-diabetic patients (Yang et al., 2013). Unlike other studies, Shaw et al. demonstrated that there was no effect of PAP therapy on glycaemic control in patients with relatively well-controlled T2DM and OSA (Shaw et al., 2016). Similarly, 3 months of CPAP treatment did not influence glycaemic control in 42 patients with OSA and T2DM (West et al., 2007). In a systematic review of nine sham-controlled studies of PAP therapy on glucose metabolism, there was no effect on glycaemic health in five studies, and

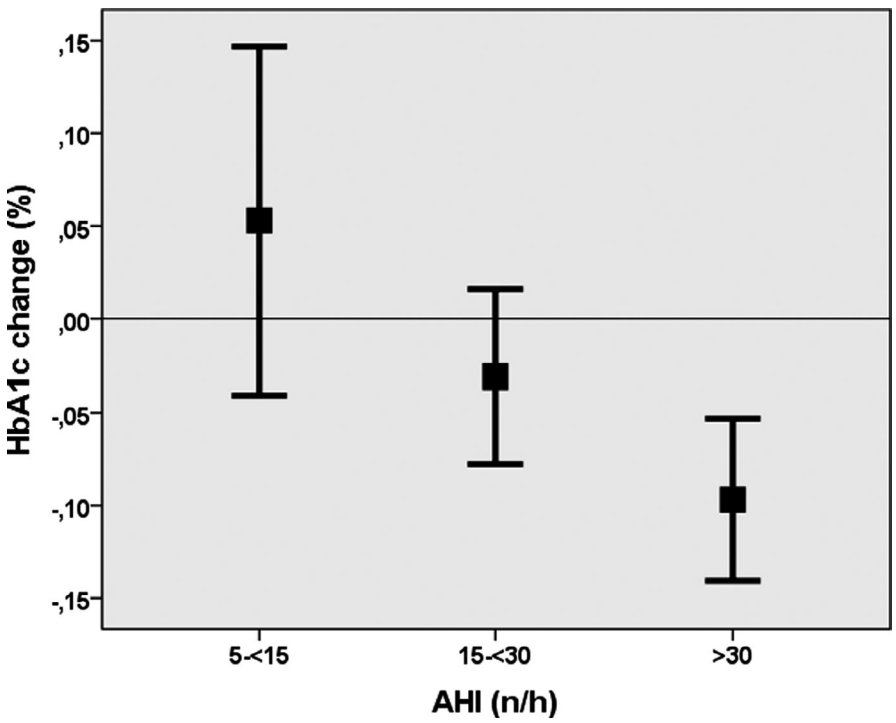

FIGURE 2 Change in glycated haemoglobin (HbA1c) levels according to OSA severity (between groups, $p = .005$). AHI, apnea–hypopnea index; OSA, obstructive sleep apnea

13652869, 2021, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jsr.13331 by University Degli Studi Di Palermo, Wiley Online Library on [26/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 Effect of OSA severity on HbA1c change in all patients

	B/L HbA1c	F/U HbA1c	Change	Within-group statistics (*p*-value)	Between-group statistics (*p*-value)
AHI classes					
5–15 (events hr^{-1})	5.84 ± 0.94	5.89 ± 1.10	0.05 ± 0.70	**.005**	**.005**
15–30 (events hr^{-1})	5.90 ± 0.90	5.87 ± 0.93	−0.03 ± 0.51		.162
≥ 30 (events hr^{-1})	6.06 ± 1.07	5.96 ± 0.97	−0.10 ± 0.68		**.005**
OSA alleviation classes					
0%–20%	5.94 ± 1.01	5.90 ± 1.05	−0.04 ± 0.72	**.034**	.052
> 20%–50%	5.91 ± 0.93	5.73 ± 0.71	−0.0.18 ± 0.51		.201
≥ 50%	6.30 ± 1.05	6.00 ± 0.75	−0.31 ± 0.98		.059

AHI, apnea–hypopnea index; B/L, baseline; F/U, follow-up; HbA1c, glycated haemoglobin; OSA, obstructive sleep apnea.

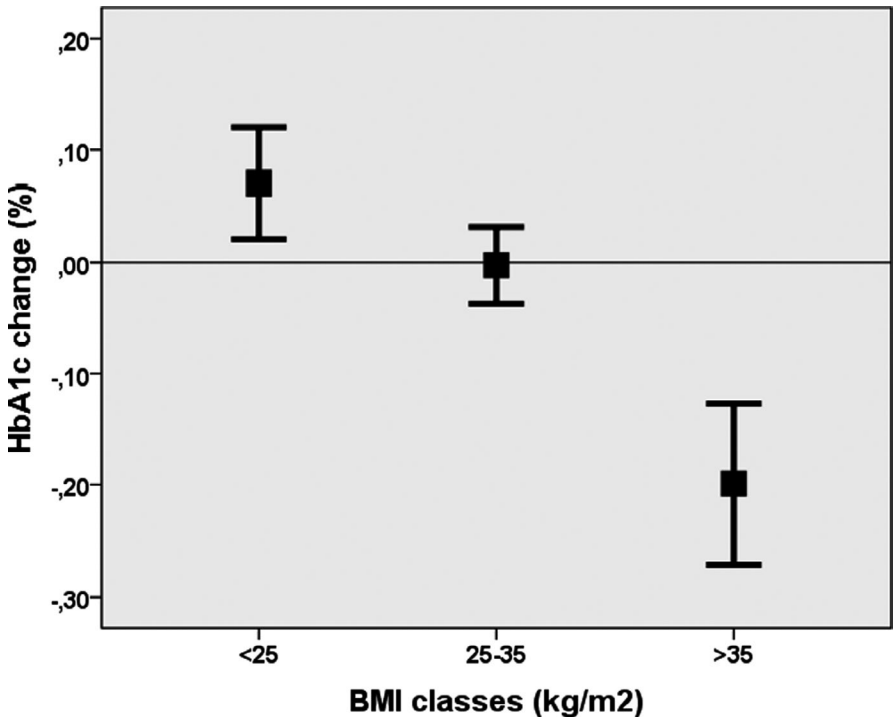

FIGURE 3 Change in glycated haemoglobin (HbA1c) levels according to BMI classes (between groups, $p < .001$). BMI, body mass index

the remaining studies reported variable results (Jullian-Desayes et al., 2015). Hence, the controlled trials do not seem to support the findings of the observational studies and not all reported PAP effects on Hb1Ac have systematically been controlled for the simultaneous change in body weight during follow up.

There are only limited data on the effect of short-term CPAP use on glycaemic control in OSA. Pamidi et al. found that CPAP treatment for 2 weeks improved glucose metabolism in patients with OSA and prediabetes (Pamidi et al., 2015). In addition, a 6-month randomized controlled trial (RCT) reported improved glycaemic control and insulin resistance after continuous (C)PAP in patients with diabetes and OSA compared with a control group (Martínez-Cerón et al., 2016). The current study identified neither adherence with nor duration of PAP use to be associated with HbA1c change. However, when adherence with PAP treatment was adjusted for habitual sleep time as well as PAP efficacy (residual AHI), we were able to establish a dose–response relationship between alleviation of OSA by PAP treatment and the improvement in glycaemic control. In addition, weight loss was found to have a strong contribution to HbA1c reduction in patients with more pronounced OSA alleviation. Hence, our data suggest that more comprehensive measures for the overall reduction of OSA burden including hypoxia and sleep fragmentation may be important in the assessment of metabolic risk reduction by treatment in patients with OSA.

The reduction of HbA1c after PAP in the present study was more pronounced in obese patients (BMI > 35 $kg\,m^{-2}$). It is possible that healthcare providers might have addressed important lifestyle changes, diet, physical activity or specific medical therapy for weight reduction particularly well in the obese OSA patients. Indeed, weight reduction at follow-up in our study cohort was more common and pronounced in the obese and morbidly obese OSA patients (Basoglu et al., 2018).

In a randomized, parallel 6-month trial examining the effects of CPAP on inflammatory markers, insulin sensitivity and lipids, there

13652869, 2021, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jsr.13331 by University Degli Studi Di Palermo, Wiley Online Library on [26/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

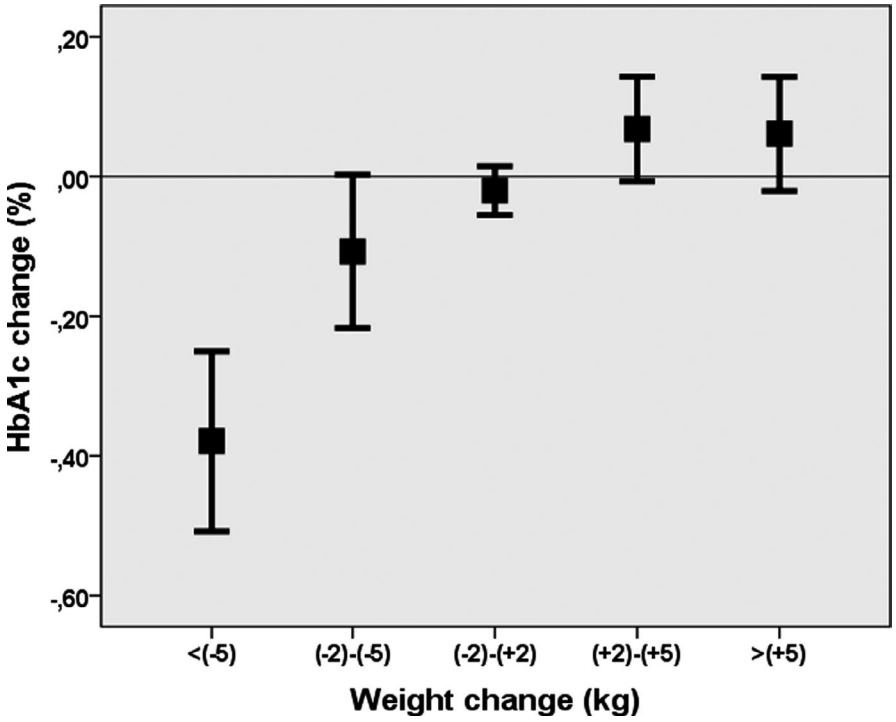

FIGURE 4 Change in glycated haemoglobin (HbA1c) levels according to weight reduction (between groups, $p < .001$)

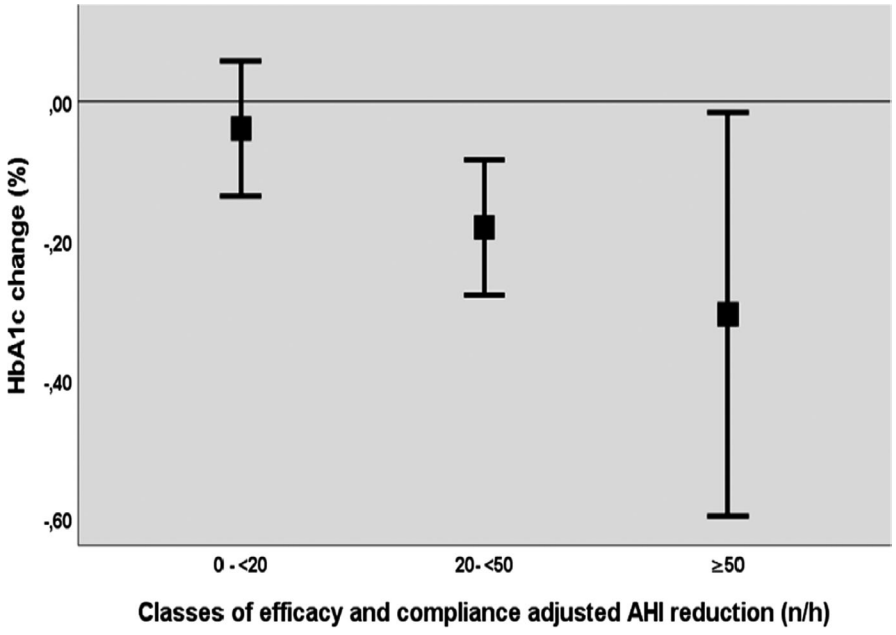

FIGURE 5 Change in glycated haemoglobin (HbA1c) according to compliance-adjusted AHI reduction (within groups $p = .034$). AHI, apnea–hypopnea index

was no clinically significant difference in reduction in C-reactive protein after 24 weeks of CPAP therapy between the CPAP alone, weight loss intervention or CPAP plus weight loss intervention groups (Chirinos et al., 2014). However, insulin sensitivity and triglycerides improved significantly in the weight loss and CPAP plus weight loss arms when compared with the CPAP alone group. In another study, it has been shown that weight loss is associated with a significant decrease in HbA1c levels in moderate and severe OSA patients who do not accept PAP therapy (Blackman et al., 2016). In our study, the most prominent predictor of HbA1c reduction was a concomitant significant weight loss. Treatment with CPAP can be used to ameliorate both conditions, as CPAP decreases hypoxia episodes, increases insulin sensitivity and improves glucose metabolism.

4.3 | Strengths and limitations

This study has several important strengths and limitations. The generalizability of the results, which originate from the large-scale, multinational and multicentric ESADA study, provides a major strength. The ESADA included a representative patient cohort, and stratification into diabetic and non-diabetic patients provided sufficient power to detect clinically meaningful differences.

13652869, 2021, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jsr.13331 by University Degli Studi Di Palermo, Wiley Online Library on [26/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 4 The robust regression model of parameters independently associated with HbA1c reduction

	β-value	Standard error	95% CI	p-value
Severe OSA	.0578	.0279	0.0031–0.1125	.038
BMI > 35 kg m^{-2}	−.1051	.0377	(−)0.1790–(−)0.0311	.005
Weight reduction > 5 kg	.2390	.0352	0.1700–0.3079	< .001

BMI, body mass index; CI, confidence interval; OSA, obstructive sleep apnea.

The major limitation of our study is the observational design without a control condition. Other measures during the follow-up period (change in lifestyle, dietary influences and repeated contact with healthcare) may have influenced glycaemic control. Those factors could not be fully controlled for in our study, and the isolated effect of PAP treatment is difficult to confirm. However, we adjusted for several confounders in our analysis, and we identified a clear dose–response relationship between OSA severity and OSA alleviation suggesting an influence of OSA on glycaemic health. The positive association between OSA alleviation by CPAP and the improvement in Hb1Ac in our study further strengthens the hypothesis that OSA treatment has beneficial effects on glycaemic control in both diabetic and obese non-diabetic patients. Nearly all diabetic patients (295/336, 87.8%) used antidiabetic drugs (oral antidiabetic or insulin) at baseline and, according to the data logged at follow-up, no major changes in antidiabetic drug intake were observed during the follow-up period. However, exact dosing schemes were not captured in our database, which clearly limits our possibilities to evaluate the impact of antidiabetic drug treatment on the HbA1c change. Another limitation is that a selection bias cannot be excluded as only a subgroup of patients is followed up in the ESADA. These are likely to be those with long-term acceptance of PAP therapy. In addition, patients with elevated Hb1Ac or diabetic subjects had a potential higher chance to be followed up with a Hb1Ac assessment during PAP treatment. However, our analysis cohort still included a substantial number of individuals (n = 305) with a low PAP compliance of < 4 hr per night and a majority of non-diabetic subjects with normal Hb1Ac levels at baseline.

Our study has important clinical implications. First, in the real-life scenario of a large multicentric cohort, very small improvements of HbA1c levels were observed for the entire OSA patient cohort. However, a number of subgroups were identified where PAP treatment was associated with clinically meaningful HbA1c reductions. The effect size of −0.24% to −0.76% Hb1Ac reductions following PAP treatment in the diabetic subgroups of our longitudinal cohort study may be compared with the mean effect of various oral antidiabetic drugs on Hb1Ac levels during RCT trials (meta-analysis results −0.5% to −1.25% Hb1Ac reduction; Sherifali et al., 2010). Oral antidiabetic medication is obviously more effective, but PAP treatment can also provide a meaningful contribution for better glycaemic control in these cardiovascular high-risk groups. Second, the evolution of body weight was the strongest factor determining the change in HbA1c over time. Despite a successful control of sleep apnea and nocturnal hypoxia, weight gain over time will blunt all potentially beneficial metabolic effects of OSA treatment. Therefore, weight control and prevention of weight gain remains an important challenge in long-term follow-up of OSA even when PAP adherence is high.

In conclusion, PAP treatment was associated with a miniature HbA1c reduction in OSA patients. A clinically relevant reduction was achieved in patients with severe OSA, in morbidly obese patients, but most obvious HbA1c decrease was found in the OSA subjects who lost more than 5 kilos during the follow-up period. Therefore, the present study underlines the importance to combine PAP use with weight reduction in OSA treatment. Although PAP treatment may have a beneficial effect on glycaemic health in subgroups of OSA patients, long-term RCTs with large sample size and after controlling confounding factors (diet, physical activity, obesity, medications, etc.) are needed.

CONFLICT OF INTEREST

All authors declare that we have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled, "**Positive airway pressure treatment reduces glycated hemoglobin (HbA1c) levels in obstructive sleep apnea patients: Longitudinal data from the ESADA**". LG reports conflicts of interest outside the submitted work: grants from Bayer, Resmed, Respironics/Philips, Desitin, the European Respiratory Society and non-financial support from Itamar Medical and Resmed; speakers bureau for Resmed, Philips, Astra Zeneca and Fisher and Paykel; patent on sleep apnea therapy issued.

AUTHOR CONTRIBUTIONS

M. S. T. had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. M. S. T., L. G. and O. K. B. contributed substantially to the study concept and design. M. S. T., L. G. and O. K. B. made substantial contributions to the acquisition, analysis, or interpretation of data for the manuscript. M. S. T., L. G. and O. K. B. contributed to the writing of the manuscript. J. H., J. A. K., J. V., W. T. N., G. R., R. T., M. R. B., T. S., P. S. and O. M. contributed to the critical revision of the manuscript before submission.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

13652869, 2021, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jsr.13331 by University Degli Studi Di Palermo, Wiley Online Library on [26/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

ORCID

Mehmet Sezai Tasbakan https://orcid.org/0000-0003-4507-9851
Ludger Grote https://orcid.org/0000-0002-7405-1682
Walter T. McNicholas https://orcid.org/0000-0001-5927-2738
Maria R. Bonsignore https://orcid.org/0000-0002-4875-7796

REFERENCES

Basoglu, O. K., Zou, D., Tasbakan, M. S., Hedner, J., Ryan, S., Verbraecken, J., Escourrou, P., Antalainen, U., Kvamme, J. A., Bonsignore, M. R., Schiza, S., Grote, L., & ESADA Study Group. (2018). Change in weight and central obesity by positive airway pressure treatment in obstructive sleep apnea patients: Longitudinal data from the ESADA cohort. *Journal of Sleep Research*, *27*(6):e12705. https://doi.org/10.1111/jsr.12705

Benjafield, A. V., Ayas, N. T., Eastwood, P. R., Heinzer, R., Ip, M. S. M., Morrell, M. J., Nunez, C. M., Patel, S. R., Penzel, T., Pépin, J. L., Peppard, P. E., Sinha, S., Tufik, S., Valentine, K., & Malhotra, A. (2019). Estimation of the global prevalence and burden of obstructive sleep apnoea: A literature-based analysis. *Lancet Respiratory Medicine*, *7*(8), 687–698. https://doi.org/10.1016/S2213-2600(19)30198-5

Blackman, A., Foster, G. D., Zammit, G., Rosenberg, R., Aronne, L., Wadden, T., Claudius, B., Jensen, C. B., & Mignot, E. (2016). Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: The SCALE Sleep Apnea randomized clinical trial. *International Journal of Obesity*, *40*(8), 1310–1319.

Chakhtoura, M., & Azar, S. T. (2012). Continuous positive airway pressure and type 2 diabetes mellitus. *Diabetes & Metabolic Syndrome*, *6*, 176–179. https://doi.org/10.1016/j.dsx.2012.09.013

Chirinos, J. A., Gurubhagavatula, I., Teff, K., Rader, D. J., Wadden, T. A., Townsend, R., Foster, G. D., Maislin, G., Saif, H., Broderick, P., Chittams, J., Hanlon, A. L., & Pack, A. I. (2014). CPAP, weight loss, or both for obstructive sleep apnea. *New England Journal of Medicine*, *370*, 2265–2275. https://doi.org/10.1056/NEJMoa1306187

Escourrou, P., Grote, L., Penzel, T., Mcnicholas, W. T., Verbraecken, J., Tkacova, R., Riha, R. L., Hedner, J., & ESADA Study Group. (2015). The diagnostic method has a strong influence on classification of obstructive sleep apnea. *Journal of Sleep Research*, *24*, 730–738. https://doi.org/10.1111/jsr.12318

Grote, L., Hedner, J., Grunstein, R., & Kraiczi, H. (2000). Therapy with nCPAP: Incomplete elimination of sleep related breathing disorder. *European Respiratory Journal*, *16*, 921–927. https://doi.org/10.1183/09031936.00.16592100

Hedner, J., Grote, L., Bonsignore, M., McNicholas, W., Lavie, P., Parati, G., Sliwinski, P., Barbe, F., De Backer, W., Escourrou, P., Fietze, I., Kvamme, J. A., Lombardi, C., Marrone, O., Masa, J. F., Montserrat, J. M., Penzel, T., Pretl, M., Riha, R., … Zielinski, J. (2011). The European Sleep Apnoea Database (ESADA): Report from 22 European sleep laboratories. *European Respiratory Journal*, *38*, 635–642. https://doi.org/10.1183/09031936.00046710

Heinzer, R., Vat, S., Marques-Vidal, P., Marti-Soler, H., Andries, D., Tobback, N., Mooser, V., Preisig, M., Malhotra, A., Waeber, G., Vollenweider, P., Tafti, M., & Haba-Rubio, J. (2015). Prevalence of sleep-disordered breathing in the general population: The HypnoLaus study. *Lancet Respiratory Medicine*, *3*(4), 310–318. https://doi.org/10.1016/S2213-2600(15)00043-0

Iber, C., Ancoli-Israeli, S., Chesson, A., & Quan, S. (2007). *The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications*, 1st ed: American Academy of Sleep Medicine.

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep*, *14*, 540–545. https://doi.org/10.1093/sleep/14.6.540

Jullian-Desayes, I., Joyeux-Faure, M., Tamisier, R., Launois, S., Borel, A. L., Levy, P., & Pepin, J. L. (2015). Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: A systematic review from sham CPAP randomized controlled trials. *Sleep Medicine Reviews*, *21*, 23–38. https://doi.org/10.1016/j.smrv.2014.07.004

Kent, B. D., Grote, L., Bonsignore, M. R., Saaresranta, T., Verbraecken, J., Lévy, P., Sliwinski, P., Tkacova, R., Kvamme, J. A., Fietze, I., Hedner, J., McNicholas, W. T. & European Sleep Apnoea Database Collaborators. (2014). Sleep apnoea severity independently predicts glycaemic health in nondiabetic subjects: The ESADA study. *European Respiratory Journal*, *44*, 130–139. https://doi.org/10.1183/09031936.00162713

Kent, B. D., Grote, L., Ryan, S., Pépin, J. L., Bonsignore, M. R., Tkacova, R., Saaresranta, T., Verbraecken, J., Lévy, P., Hedner, J., & McNicholas, W. T. (2014). Diabetes mellitus prevalence and control in sleep-disordered breathing: The European Sleep Apnea Cohort (ESADA) study. *Chest*, *146*, 982–990. https://doi.org/10.1378/chest.13-2403

Lattimore, J. D., Celermajer, D. S., & Wilcox, I. (2003). Obstructive sleep apnea and cardiovascular disease. *Journal of the American College of Cardiology*, *41*, 1429–1437. https://doi.org/10.1016/s0735-1097(03)00184-0

Loffler, K. A., Heeley, E., Freed, R., Meng, R., Bittencourt, L. R., Gonzaga Carvalho, C. C., Chen, R., Hlavac, M., Liu, Z., Lorenzi-Filho, G., Luo, Y., McArdle, N., Mukherjee, S., Yap, H. S., Zhang, X., Palmer, L. J., Anderson, C. S., McEvoy, R. D., Drager, L. F., & SAVE Substudy Investigators. (2020). Continuous positive airway pressure treatment, glycemia, and diabetes risk in obstructive sleep apnea and comorbid cardiovascular disease. *Diabetes Care*, *43*(8), 1859–1867. https://doi.org/10.2337/dc19-2006

Malik, J. A., Masoodi, S. R., & Shoib, S. (2017). Obstructive sleep apnea in type 2 diabetes and impact of continuous positive airway pressure therapy on glycemic control. *Indian Journal of Endocrinology and Metabolism*, *21*, 106–112. https://doi.org/10.4103/2230-8210.196005

Martínez-Cerón, E., Barquiel, B., Bezos, A. M., Casitas, R., Galera, R., García-Benito, C., Hernanz, A., Alonso-Fernández, A., & Garcia-Rio, F. (2016). Effect of continuous positive airway pressure on glycemic control in patients with obstructive sleep apnea and type 2 diabetes. A randomized clinical trial. *American Journal of Respiratory and Critical Care Medicine*, *194*, 476–485. https://doi.org/10.1164/rccm.201510-1942OC

Nagayoshi, M., Punjabi, N. M., Selvin, E., Pankow, J. S., Shahar, E., Iso, H., Folsom, A. R., & Lutsey, P. L. (2016). Obstructive sleep apnea and incident type 2 diabetes. *Sleep Medicine*, *25*, 156–161. https://doi.org/10.1016/j.sleep.2016.05.009

Nathan, D. M. & DCCT/EDIC Research Group. (2014). The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: Overview. *Diabetes Care*, *37*(1), 9–16. https://doi.org/10.2337/dc13-2112

Pamidi, S., & Tasali, E. (2012). Obstructive sleep apnea and type 2 diabetes: Is there a link? *Frontiers in Neurology*, *3*, 126. https://doi.org/10.3389/fneur.2012.00126

Pamidi, S., Wroblewski, K., Stepien, M., Sharif-Sidi, K., Kilkus, J., Whitmore, H., & Tasali, E. (2015). Eight hours of nightly continuous positive airway pressure treatment of obstructive sleep apnea improves glucose metabolism in patients with prediabetes. A randomized controlled trial. *American Journal of Respiratory and Critical Care Medicine*, *192*, 96–105. https://doi.org/10.1164/rccm.201408-1564OC

Schlatzer, C., Schwarz, E. I., & Kohler, M. (2014). The effect of continuous positive airway pressure on metabolic variables in patients with obstructive sleep apnoea. *Chronic Respiratory Disease*, *11*, 41–52. https://doi.org/10.1177/1479972313516882

Shaw, J. E., Punjabi, N. M., Naughton, M. T., Willes, L., Bergenstal, R. M., Cistulli, P. A., Fulcher, G. R., Richards, G. N., & Zimmet, P. Z. (2016). The effect of treatment of obstructive sleep apnea on glycemic control in type 2 diabetes. *American Journal of Respiratory and Critical Care Medicine*, *19*, 486–492. https://doi.org/10.1164/rccm.201511-2260OC

Sherifali, D., Nerenberg, K., Pullenayegum, E., Cheng, J. E., & Gerstein, H. C. (2010). The effect of oral antidiabetic agents on A1C levels:

13652869, 2021, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jsr.13331 by University Degli Studi Di Palermo, Wiley Online Library on [26/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

A systematic review and meta-analysis. *Diabetes Care*, *33*(8), 1859–1864. https://doi.org/10.2337/dc09-1727

Standards of Practice Committee of the American Sleep Disorders Association. (1994). Practice parameters for the use of portable recording in the assessment of obstructive sleep apnea. *Sleep*, *17*, 372–377. https://doi.org/10.1093/sleep/17.4.372

West, S. D., Nicoll, D. J., Wallace, T. M., Matthews, D. R., & Stradling, J. R. (2007). Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. *Thorax*, *62*, 969–974. https://doi.org/10.1136/thx.2006.074351

Yang, D., Liu, Z., Yang, H., & Luo, Q. (2013). (2013) Effects of continuous positive airway pressure on glycemic control and insulin resistance in patients with obstructive sleep apnea: A meta-analysis. *Sleep and Breathing*, *17*, 33–38. https://doi.org/10.1007/s11325-012-0680-8

APPENDIX

ESADA COLLABORATORS

1. Erna Petiet, Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium
2. Georgia Trakada, Pulmonary Medicine, National and Kapodistrian University of Athens, Athens, Greece
3. Ingo Fietze, Schlafmedizinisches Zentrum, Charité – Universitätsmedizin Berlin, Germany
4. Thomas Penzel, Schlafmedizinisches Zentrum, Charité – Universitätsmedizin Berlin, Germany
5. Naima Laharnar, Schlafmedizinisches Zentrum, Charité – Universitätsmedizin Berlin, Germany
6. Ondrej Ludka, Department of Cardiology, University Hospital Brno and International Clinical Research Center, St. Ann´s University Hospital, Brno, Czech Republic
7. Izolde Bouloukaki, Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Greece
8. Sophia Schiza, Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Greece
9. Silke Ryan, Pulmonary and SleepDisorders Unit, St. Vincent's University Hospital, Dublin, Ireland
10. Renata L. Riha, Department of Sleep Medicine, Royal Infirmary Edinburgh, Scotland
11. Ding Zou, Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Göteborg, Sweden
12. Sebastien Bailly, Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France
13. JeanLouis Pépin, Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France
14. Holger Hein, Sleep Disorders Center, St. Adolf Stift, Reinbeck, Germany
15. Jitka Buskova, Department of Sleep Medicine, National Institute of Mental Health, Klecany, Czech Republic
16. Pavol Joppa, Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P.J.Safarik University and L. Pasteur University Hospital, Kosice, Slovakia
17. Richard Staats, Department of Respiratory Medicine, Hospital de Santa Maria, Lisbon, Portugal
18. Dries Testelmans, Sleep Disorders Centre, University Hospital Gasthuisberg, Leuven, Belgium
19. Haralampos Gouveris, ENT department at Mainz University Hospital, Mainz, Germany
20. Carolina Lombardi, Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, St. Luke Hospital, Milan & Department of Medicine and Surgery; University of Milano-Bicocca, Milan, Italy.
21. Gianfranco Parati, Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, St. Luke Hospital, Milan & Department of Medicine and Surgery; University of Milano-Bicocca, Milan, Italy.
22. Francesco Fanfulla, Unità Operativa di Medicina del Sonno, Istituto Scientifico di Pavia IRCCS, Pavia, Italy
23. Michel Petitjean, Unité de Médecine du Sommeil, Hopital Antoine-Beclere, Clamart, France
24. Marta Drummond, Pulmonology Department Hospital São João, Medicine Faculty of Porto University, Porto, Portugal
25. Mafalda van Zeller, Pulmonology Department Hospital São João, Medicine Faculty of Porto University, Porto, Portugal
26. Simon Herkenrath, Sleep Disorders Centre, Pulmonary Clinic, Solingen, Germany
27. Winfried Randerath, Sleep Disorders Centre, Pulmonary Clinic, Solingen, Germany
28. Zoran Dogas, Sleep Medicine Center, Department of Neuroscience, University of Split School of Medicine, Split, Croatia
29. Tea Galic, Sleep Medicine Center, Department of Neuroscience, University of Split School of Medicine, Split, Croatia
30. Athanasia Pataka, Respiratory Failure Unit, G. Papanikolaou Hospital, Thessalonika, Greece
31. Stefan Mihaicuta, Pulmonary Department, Victor Babes University of Medicine and Pharmacy, Victor Babes Hospital, Timisoara, Rumania
32. Ulla Anttalainen, Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland
33. Pawel Sliwinski, 2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
34. Robert Plywaczewski, 2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland

How to cite this article: Tasbakan MS, Grote L, Hedner J, et al. Positive airway pressure (PAP) treatment reduces glycated hemoglobin (HbA1c) levels in obstructive sleep apnea patients with concomitant weight loss: Longitudinal data from the ESADA. *J Sleep Res*. 2021;30:e13331. https://doi.org/10.1111/jsr.13331

13652869, 2021, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jsr.13331 by University Degli Studi Di Palermo, Wiley Online Library on [26/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License