

This item is the archived peer-reviewed author-version of:

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

Reference:

Tasbakan Mehmet Sezai, Grote Ludger, Hedner Jan, Kvamme John Arthur, Verbraecken Johan, McNicholas Walter T., Roisman Gabriel, Tkacova Ruzena, Bonsignore Maria R., Saaresranta Tarja,- Positive airway pressure (PAP) treatment reduces glycated hemoglobin (HbA1c) levels in obstructive sleep apnea patients with concomitant weight loss : longitudinal data from the ESADA
Journal of sleep research - ISSN 0962-1105 - Hoboken, Wiley, 30:5(2021), e13331
Full text (Publisher's DOI): <https://doi.org/10.1111/JSR.13331>
To cite this reference: <https://hdl.handle.net/10067/1783530151162165141>

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

M. Sezai Tasbakan¹, Ludger Grote², Jan Hedner², John-Arthur Kvamme³, Johan Verbraecken⁴, Walter T. McNicholas⁵, Gabriel Roisman⁶, Ruzena Tkacova⁷, Maria R. Bonsignore⁸, Tarja Saaresranta⁹, Paschalis Steiropoulos¹⁰, Ozen K. Basoglu¹

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

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

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

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

⁵Department of Respiratory Medicine, St Vincent's University Hospital, University College Dublin, Dublin, Ireland

⁶Sleep Disorders Centre, Hospital Antoine-Becclere, Clamart, France

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

⁸PROMISE Dept, University of Palermo, Palermo, Italy

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

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

Word count:

Abstract: 243

Running text (excluding references and figure legends): 2729

Corresponding author

M. Sezai Tasbakan, MD, Professor

Ege University, Faculty of Medicine

Department of Chest Disease, Izmir, Turkey

E-mail: sezai.tasbakan@ege.edu.tr, sezai72000@yahoo.com

ABSTRACT

Introduction

Patients with obstructive sleep apnea (OSA) are at increased risk of developing metabolic disease such as diabetes mellitus. Positive airway pressure (PAP) therapy reduces apneas but the effects of PAP on glycemic control remain unknown. We therefore evaluated the change in glycated hemoglobin (Hb1Ac) in a large prospective cohort of OSA patients after long-term treatment with PAP.

Method

HbA1c levels were assessed in a subsample of the European Sleep Apnea Database (ESADA) [n=1608 OSA patients recruited from 13 centers, 74.2% males, mean age 53.9±10.8 years, body mass index (BMI) 32.8±7.0 kg/m² and apnea-hypopnea index (AHI) 40.4±24.5 events/h] at baseline and at long-term follow up with PAP therapy (mean 378.9±423.0 days). In regression analysis, treatment response was controlled for important confounders.

Results

Hb1Ac was reduced from 5.98±1.01% to 5.93±0.98% (n=1608, p=0.001). Patient subgroups with more pronounced HbA1c response included diabetic patients (-0.152±1.022, p=0.019), severe OSA at baseline (AHI≥30/h) (-0.097±0.678, p=0.005), morbidly obese patients (BMI≥35kg/m²) (-0.199±0.814, p<0.001), and patients using auto-adjusting PAP (-0.115±0.709, p=0.030). The strongest HbA1c reduction was observed in patients with concomitant weight reduction >5 kilos (-0.379±0.988, p<0.001). In multivariate analysis, severe OSA (p=0.038), morbid obesity (p=0.005), auto-adjusting PAP therapy (p<0.001), and weight reduction >5 kilos (p<0.001) were independently associated with a HbA1c reduction.

Conclusion

Overall, HbA1c reduction was clinically relevant in morbidly obese OSA patients and after significant weight loss. Our study underlines the importance to combine PAP use with lifestyle adjustments in order to substantially modify metabolic complications in OSA.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by an instability of the upper airway during sleep resulting in a reduction of airflow, oxygen desaturation, and sleep disruption. OSA affects 3.9% of women and 8.8% of men between the ages of 30 and 70 year (1). Individuals with OSA have an increased risk of developing a number of comorbidities including cardiometabolic disease such as hypertension and diabetes mellitus (2, 3). With regard to diabetes, evidence from a number of studies suggests that 15-30% of individuals with OSA have type 2 diabetes mellitus (T2DM) and that OSA is an independent risk factor for this comorbidity (4). A variety of potential mechanisms have been proposed to explain the link between OSA and disturbed glucose metabolism and the development of T2DM. These mechanisms include activation of the sympathetic nervous system by intermittent hypoxia and sleep fragmentation. Further, 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 patients (5).

Positive airway pressure (PAP) therapy is the gold standard treatment for OSA. Although PAP can be a very effective therapy for OSA, the effects of such treatment on insulin sensitivity and glycemic control in T2DM is not sufficiently 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 glycemic health and the remaining studies reported variable results. In conclusion, the controlled trials could not support the findings of the observational studies (6,7). But these trials were hampered by a short treatment duration and a very small sample size.

In the setting of the large, prospective ESADA cohort study we aimed to assess the effects of PAP on glycemic control. It is hypothesized that the long-term reduction of overnight sympathetic activation and intermittent hypoxia by PAP treatment will improve insulin sensitivity and thereby the elevated blood glucose levels previously demonstrated in OSA patients. We also hypothesize that PAP effects are more pronounced in patients with severe sleep apnea and comorbid obesity as both hypoxic burden and sympathetic activity are more pronounced in those individuals. We opted to study the PAP effects on glycated hemoglobin (HbA1c), a well-established parameter for glycemic control during the past 3 months, in several OSA phenotypes.

MATERIALS AND METHODS

The European Sleep Apnea Database (ESADA) study is a pan-European, multicenter, prospective study and the current analysis included data from 33 sleep clinics across 19 countries (8). 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 centers to the central database at the University of Gothenburg.

Patients

Sleep apnea patients on current treatment with PAP, aged 18 years and above, with an assessment of Hb1Ac at baseline and during PAP follow up, have been enrolled in the ESADA from March 2007 to December 2017 (n=1608). Patients referred for assessment at any of the participating centers were considered eligible for enrollment in ESADA, unless they were receiving treatment of previously diagnosed OSA, had ongoing substance abuse, or had severe comorbidity with short life expectancy. At baseline, demographic, anthropometric, and clinical variables, including measured BMI, smoking history, comorbidities, and medication usage, were recorded for each patient. Participating patients also provided a venous blood sample for assessment of HbA1c levels. The patients used PAP treatment for at least 3 months. Research ethics committee approval for the study was obtained at each of the participating centers. Oral and written informed consent was obtained from all participants.

Sleep Studies

A detailed description of the sleep study methodology in the ESADA has been published previously (9). Either cardiorespiratory polygraphy (PG, n=4) or full polysomnography (PSG, n=1604) were performed according to local practice. All sleep data were manually edited according to protocol definitions. PG recordings included a minimum of four recording channels (level 3 devices according to the American Academy of Sleep Medicine [AASM]), (10) while PSG studies were performed and analyzed 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 oxyhemoglobin desaturation index (ODI, desaturation criteria of 4%) were defined per hour of sleep for PSG and per hour of analyzed time for PG recordings (11). The Epworth Sleepiness Scale (ESS) was used to assess subjective daytime sleepiness (12). Sleep study scoring in ESADA has been discussed in more detail previously (8, 9).

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 bilevel), 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.

Description of the OSA alleviation calculation: OSA alleviation, a measure of overall OSA reduction by PAP therapy including PAP compliance in relation to habitual sleep time and residual AHI (13), was computed for all patients.

Analysis of data

Statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM, Armonk, NY, USA). The primary end point was the change in HbA1c measured after at least 3 months of PAP treatment (Paired students t-test, entire study population). In order to further explore the PAP treatment effects, we performed analysis of the Hb1Ac change by PAP by means of the paired t-test for different OSA severity classes (mild, moderate, severe OSA according to clinical AHI cut off's of 5-<15, 15-<30, and ≥ 30 events/hour of sleep). Differences between different OSA phenotypes (using the change from baseline as the outcome variable) were assessed with the unpaired Student t test. Baseline patient characteristics were compared for diabetic and non-diabetic subjects. The robust regression analysis procedure (SAS statistical program) was used for linear regression analysis.

RESULTS

Main analysis of change in HbA1c levels at follow-up

From March 2007 to December 2017, 22851 subjects were enrolled in the ESADA database. A total of 5079 of these patients were diagnosed with OSA and given PAP therapy. A total of 1608 patients used PAP device more than 90 days and the assessment of HbA1c was performed at both baseline and follow-up (Figure 1). Separate analysis was performed in diabetic (n=336) and on-diabetic subjects (n=1272). Demographic and clinical data of the total study population and the diabetic and non-diabetic subpopulations are given in Table 1. For the entire study group, HbA1c decreased significantly with PAP therapy at follow-up (5.98 ± 1.01 vs 5.93 ± 0.98 , $p=0.001$).

Factors influencing the change in HbA1c during long-term PAP treatment

Gender

Diabetes mellitus was more prevalent in female than in male patients (29.5% vs. 18.0% , $p<0.001$). Baseline HbA1c levels were higher in female compared with male OSA patients (6.13 ± 1.11 vs 5.93 ± 0.97 ; $p=0.003$, respectively). However, HbA1c was significantly reduced in both groups (-0.04 in males and -0.10 in females, $p<0.001$, respectively) and did not show a gender difference ($p=0.116$).

Sleep apnea severity

The change in HbA1c varied between OSA groups (Table 2). HbA1c levels decreased more pronounced in patients with severe OSA ($AHI \geq 30$ events/h) at baseline when compared to mild OSA patients (Table 2, figure 2).

Body weight

HbA1c decline was most pronounced in OSA patients with morbid obesity (-0.20 ± 0.81 kg, $p<0.001$) (Figure 3). In contrast, HbA1c level increased in normal weighted OSA patients ($BMI < 25$ kg/m²) during the treatment period.

All patients were classified into five groups according to the observed weight change during the follow-up period. The change in weight had major influence on HbA1c in all patients. The largest HbA1c decrease was observed in patients with a concomitant weight loss of >5 kg, whereas weight increase was associated with a HbA1c increase despite ongoing PAP therapy (Figure 4).

Type of PAP device

HbA1c reduction was more pronounced in patients treated with auto-adjusting PAP (APAP) device compared to those on continuous PAP (CPAP) treatment (-0.115 vs -0.025 , $p=0.016$, figure 5).

Compliance and duration of PAP device

All patients were classified according to compliance (hours of use per night) with and duration (PAP duration more than one year was called as long-term) of PAP treatment. We found that duration of nightly use and long-term PAP treatment had no additional benefit on HbA1c ($p=0.917$ and $p=0.978$, respectively). In contrast, the calculated parameter “OSA alleviation”, which accounted for PAP compliance, habitual sleep time and efficacy of PAP treatment (residual AHI), showed a dose response relationship between change in Hb1Ac levels and adjusted PAP treatment efficacy. Only OSA patients with >50% OSA alleviation with PAP treatment showed a significant HbA1c reduction when compared to individuals with OSA alleviation 0-20% and 20-50% (-0.307 ± 0.978 vs -0.039 ± 0.715 and -0.182 ± 0.512 , $p=0.034$) (Table 2).

Diagnosis of diabetes mellitus

Factors influencing the HbA1c changes in diabetic and non-diabetic patients were evaluated in detail (Table 3). In general, HbA1c reduction was more prominent in patients with DM compared with non-DM patients ($p=0.036$). In patients with DM, significantly stronger HbA1c reduction was observed in those individuals with severe OSA, morbid obese and a weight reduction of more than 5 kilos during follow up ($p=0.002$, $p<0.001$ and $p<0.001$, respectively).

Predictors of HbA1c decrease with PAP treatment

Univariate analysis performed in the entire study population of 1608 OSA patients demonstrated that a DM diagnosis, OSA severity, obesity, type of PAP device, and weight reduction were significantly associated with HbA1c reductions (all $p<0.05$). In the multivariate robust regression model, treatment with APAP ($p<0.001$), morbid obesity ($p=0.005$), severe OSA ($p=0.038$) and weight reduction more than 5 kilos ($p<0.001$) were independently associated with HbA1c reduction (Table 4).

DISCUSSION

In the largest prospective cohort study to date, we observed an association between long-term PAP therapy and improved glycemic health. This association was proven in both diabetic and non-diabetic OSA patients. A dose-response relationship between both OSA severity at baseline and overall OSA alleviation with PAP treatment on one hand and the improvement in Hb1Ac on the other hand was established. However, we quantified the strong impact of obesity at baseline and body weight change during treatment as most powerful confounders. Clinically meaningful Hb1Ac reductions can only be achieved in patients with concomitant weight reduction during PAP treatment. Our study was performed in a multinational population of OSA subjects across Europe which increases the impact and generalizability of our findings. Interestingly, auto-adjusting PAP use was associated with Hb1Ac reduction.

Sleep apnea and glycemic health

In the cross-sectional analysis of our ESADA Cohort HbA1c levels in nondiabetic subjects were independently associated with OSA severity. (14). Subsequently, T2DM prevalence was also studied in this cohort. It was shown that increasing OSA severity is associated with increased likelihood of concomitant T2DM and worse diabetic control in patients with T2DM (15). In line with these findings, we also found in the present study higher baseline HbA1c levels in severe OSA patients compared to mild-to-moderate OSA patients. Similarly, the prevalence of severe OSA was higher in patients with diabetes.

OSA treatment and glycemic health

Malik et al. (16) assessed the prevalence and severity of OSA in T2DM patients, and the impact of OSA treatment on HbA1c. They showed that 59% of 62 diabetic patients on PAP treatment had improvement in their glycemic control as measured by HbA1c. In another study, the effect of PAP therapy on HbA1c levels in patients with sub-optimally controlled diabetes and OSA was assessed. In 26 patients with OSA and T2DM, 6-month PAP treatment resulted in improved glycemic control and insulin resistance compared with the control group who had no PAP therapy (17). In the present study, we found that HbA1c decreased both in patients with and without diabetes at follow-up, whereas more prominent HbA1c decrease was observed in OSA patients with T2DM. In patients with diabetes, severe OSA was observed more often in our study population, and HbA1c reduction was significant in severe OSA patients. So, it could be speculated that the patients with high values of HbA1c could benefit more from PAP treatment. There is not enough data in the literature on this subject. In a meta-analysis of uncontrolled studies, PAP treatment was also found to improve glucose metabolism both in diabetic and non-diabetic patients (6). Unlike other studies, Shaw et al. (18) demonstrated that there was no effect of PAP therapy on glycemic control in patients with relatively well-controlled T2DM and OSA. In another study, 42 patients with OSA and T2DM were treated with CPAP for 3 months and CPAP treatment did not significantly improve measures of glycemic control or insulin resistance (19). Besides, a systematic review summarized nine sham-controlled studies evaluating the effect of

PAP therapy on glucose metabolism (20). Five studies showed no effects on different markers of glycemic health and the remaining studies reported variable results. In conclusion, the controlled trials could not support the findings of the observational studies.

There was no data about effect of nightly, short- or long-term CPAP use on glycemic control in OSA patients. Pamidi et al. (21) found that 8-hour nightly CPAP treatment for 2 weeks improved glucose metabolism in patients with OSA and prediabetes. They concluded that CPAP treatment may be beneficial for metabolic risk reduction. In a randomized clinical trial, CPAP effect in a 6-month was evaluated in 50 patients with OSA and T2DM (two HbA1c levels equal to or exceeding 6.5%). Among patients with diabetes and OSA, CPAP treatment resulted in improved glycemic control and insulin resistance compared with the results of a control group (17). In this study, we classified all patients according to compliance (hours of use per night) and duration (PAP duration more than one year was called as long-term) of PAP treatment. We found that duration of nightly use and long-term PAP treatment had no additional benefit on HbA1c. However, when we adjusted for compliance adjusted for habitual sleep time as well as for PAP efficacy, we could establish a dose response relationship between PAP efficacy and improvement in glycemic control.

The effect of CPAP treatment on glucose metabolism was evaluated in 80 morbidly obese OSA patients and the improvement of glucose tolerance in morbidly obese patients with severe OSA was detected (22). This result supports an improvement in peripheral insulin resistance after CPAP treatment. Similarly, HbA1c decrease after PAP treatment were important in obese patients (BMI>35) in the present study. This result could be explained by higher prevalence of diabetes and HbA1c levels in obese patients. Besides, the patients and their health care providers might stress the importance of lifestyle changes, diet, physical activity and specific medical therapy for weight reduction in obese OSA patients. Indeed, weight reduction at follow up in our study cohort was more common and pronounced in the obese and morbid obese OSA patients (23).

In a randomized, parallel 6-month trial examining the effects of CPAP on inflammatory markers, insulin sensitivity and lipids, there was no clinically significant reduction in CRP after 24 weeks CPAP therapy between CPAP alone, weight loss intervention or CPAP plus weight loss intervention groups. However, insulin sensitivity and triglycerides significantly improved in the weight loss and CPAP plus weight loss arms when compared to CPAP alone (24). In our study, the most prominent HbA1c decrease was observed in patients with weight lost more than 5 kilos, and weight reduction was the strongest predictor of HbA1c change. Treatment with CPAP can be used to ameliorate both conditions, as CPAP decreases hypoxia episodes, increases insulin sensitivity and improves glucose metabolism. Weight-loss strategies play an critical role in improving T2DM, and other associated comorbidities in OSA patients.

So far, the effect of PAP devices type on HbA1c reduction in patients with OSAS has not been evaluated. In our study, treatment with auto-adjusting PAP were found to be independently associated with HbA1c reduction. This is in contrast to the findings in other studies which showed better sleep

quality, better blood pressure control, and improved preservation of renal function in patients treated with CPAP compared with APAP (25-27). The reason of our finding on improved glycemic control while using APAP instead of CPAP devices is not known and our study design does not allow for a detailed analysis of potential pathophysiological mechanisms behind this finding. However, overall OSA alleviation was higher in APAP use compared to CPAP use and it might be speculated that small improvement in hypoxic burden during sleep may have contributed to this finding. Another possible explanation might be that unexplored confounders like center differences in diabetic care have influenced the finding.

Strengths and limitations

There are several strengths and limitations of our study. The generalizability of the results originating from the multinational and multicenter study design as well as the large cohort constitutes a major strength. Indeed, our data clearly showed stronger associations between PAP treatment and HbA1c reduction in the subgroups of OSAS patients such as severe OSAS, obese patients and patients with weight reduction. One of the other strengths of our study is that it is the first study that evaluated effect of different PAP modes. On the other hand, some important confounders that could influence the association between PAP treatment effect and glycemic status like diet and lifestyle changes over time could not be fully controlled in the present study.

Our study has important clinical implications. First, in the real life scenario of a large multicentric cohort, very small improvements of Hb1Ac levels were observed. However, a number of subgroups were identified where PAP treatment was associated with clinically meaningful Hb1Ac reductions. These subgroups included patients with existing diabetes mellitus, obese patients and patients with severe OSA. All those subgroups have in common, that they are characterized by an increased risk for later cardio- and cerebrovascular complications. Rigorous treatment of OSA may be therefore specifically important for risk factor reduction in this high risk group. Second, the evolution of body weight was one strong factor determining the change in Hb1Ac levels over time. Despite the highly successful control of sleep apnea and nocturnal hypoxia, weight gain over time will blunt all beneficial effects of OSA treatment. Therefore, weight control and managing of weight gain remains a large challenge in the long-term follow up of OSA even when PAP compliance is high. Finally, our data show for the first time that treatment with APAP may have more beneficial effects on glycemic health when compared with OSA treatment using the CPAP mode. Although APAP treatment mode was not associated with higher compliance compared with CPAP mode, our finding may be explained by a better adaptation of the APAP therapy mode to night to night variability of OSA severity. Further, APAP is sensitive to the treatment of flow restriction and snoring which may have an impact on sleep structure and metabolic control. However, despite a rigorous control of potential confounders in our

regression model, we cannot rule out that other factors - not yet included in our current analysis - might explain the more pronounced Hb1Ac reduction in patients treated with APAP.

In conclusion, PAP treatment was independently associated with HbA1c reduction in OSA patients. A clinically relevant reduction was achieved in patients with severe OSA, in morbidly obese patients, and in the OSA subjects who lost weight more than 5 kilos during the follow up period. Besides, auto-titrating PAP use was associated with significant Hb1Ac reduction.

Table 1. Characteristics of the diabetic and non-diabetic OSA patients

Parameter	Total (n=1608)	Diabetic OSA patients (n=336)	Non-diabetic OSA patients (n=1272)	Between group comparisons (p value)
Age (yrs)	53.9±10.8	57.3±9.1	53.0±10.0	<0.001
Male gender, n (%)	1193 (74.2)	214 (63.7)	979 (77.0)	<0.001
Current smoker, n (%)	371 (23.1)	69 (20.5)	302 (23.7)	0.121
BMI (kg/m ²)	32.8±7.0	36.0±7.7	31.9±6.3	<0.001
Co-morbid diseases				
Hypertension, n (%)	779 (48.4)	251 (74.7)	528 (41.7)	<0.001
Coronary artery disease, n (%)	169 (10.5)	99 (7.8)	70 (20.8)	<0.001
Hyperlipidemia, n (%)	523 (32.5)	149 (44.3)	374 (29.5)	<0.001
COPD, n (%)	75 (4.7)	22 (6.5)	53 (4.2)	0.05
ESS score	10.1±5.1	10.4±5.2	10.1±5.0	0.355
AHI (events/h)	40.4±24.5	43.2±25.5	39.6±24.2	<0.018
Baseline HbA1c (%)	5.98±1.01	7.14±1.29	5.67±0.63	<0.001
Follow-up HbA1c (%)	5.93±0.98	6.98±1.36	5.65±0.59	<0.001
Mean PAP duration (days)	378.9±423.0	298.2±384.2	400.2±430.3	<0.001
Mean PAP compliance (h)	5.3±2.0	5.2±2.1	5.3±1.9	0.258

AHI, apnea-hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESS, Epworth sleepiness scale; OSA, obstructive sleep apnea; PAP, positive airway pressure

Table 2. Effect of OSA severity on HbA1c change in all patients

AHI classes	B/L HbA1c	F/U HbA1c	Change	Within group statistics (p value)	Between group statistics (p value)
5-15 (events/h)	5.84±0.94	5.89±1.10	0.050±0.698	0.005	0.005
15-30 (events/h)	5.90±0.90	5.87±0.93	-0.031±0.514		0.162
≥30 (events/h)	6.06±1.07	5.96±0.97	-0.097±0.678		0.005
OSA alleviation classes					
0-20%	5.94±1.01	5.90±1.05	-0.039±0.715	0.034	0.052
>20-50%	5.91±0.93	5.73±0.71	-.0.182±0.512		0.201
=>50%	6.30±1.05	6.00±0.75	-0.307±0.978		0.059

AHI= apnea-hypopnea index; B/L=baseline; F/U= follow-up; OSA= obstructive sleep apnea

Table 3. Change in HbA1c according to DM presence

	Patients with DM (n=336)	Patients without DM (n=1272)	Within group difference pre-, post-treatment DM patients (p value)	Within group difference pre-, post-treatment Non-DM patients (p value)	Between group difference (p value)
HbA1c (%) change	-0.152	-0.033	0.007	0.016	0.036
AHI classes					
5-15 events/h	+0.112	+0.039			NS
15-30 events/h	-0.076	-0.020	0.095	0.055	NS
≥30 events/h	-0.239	-0.057			0.002
BMI classes					
<25 kg/m ²	+0.220	+0.064			0.012
25-35 kg/m ²	+0.055	-0.015	<0.001	0.001	NS
>35 kg/m ²	-0.384	-0.111			<0.001
Weight change					
< (-5) kg	-0.763	-0.242			<0.001
(-2)-(-5) kg	+0.053	-0.158			NS
(-2)-(+2) kg	-0.093	-0.001	<0.001	<0.001	NS
(+2)-(+5) kg	+0.190	+0.039			NS
> (+5) kg	+0.103	+0.053			NS
PAP mode					
APAP	-0.330	-0.073	0.107	0.048	0.016
CPAP	-0.081	-0.010			

AHI, apnea-hypopnea index; APAP, auto-adjusting positive airway pressure; BMI, body mass index; CPAP, continuous positive airway pressure; DM, diabetes mellitus

Table 4. The multivariate robust regression model of parameters independently associated with HbA1c reduction.

	β value	Standart error	95% CI	p value
Treatment with APAP	0.0759	0.0200	0.0368-0.1151	<0.001
Severe OSA	0.0578	0.0279	0.0031-0.1125	0.038
BMI>35 kg/m ²	-0.1051	0.0377	(-)0.1790-(-)0.0311	0.005
Weight reduction> 5 kg	0.2390	0.0352	0.1700-0.3079	<0.001

APAP, auto-adjusting positive airway pressure; BMI, body mass index; OSA= obstructive sleep apne

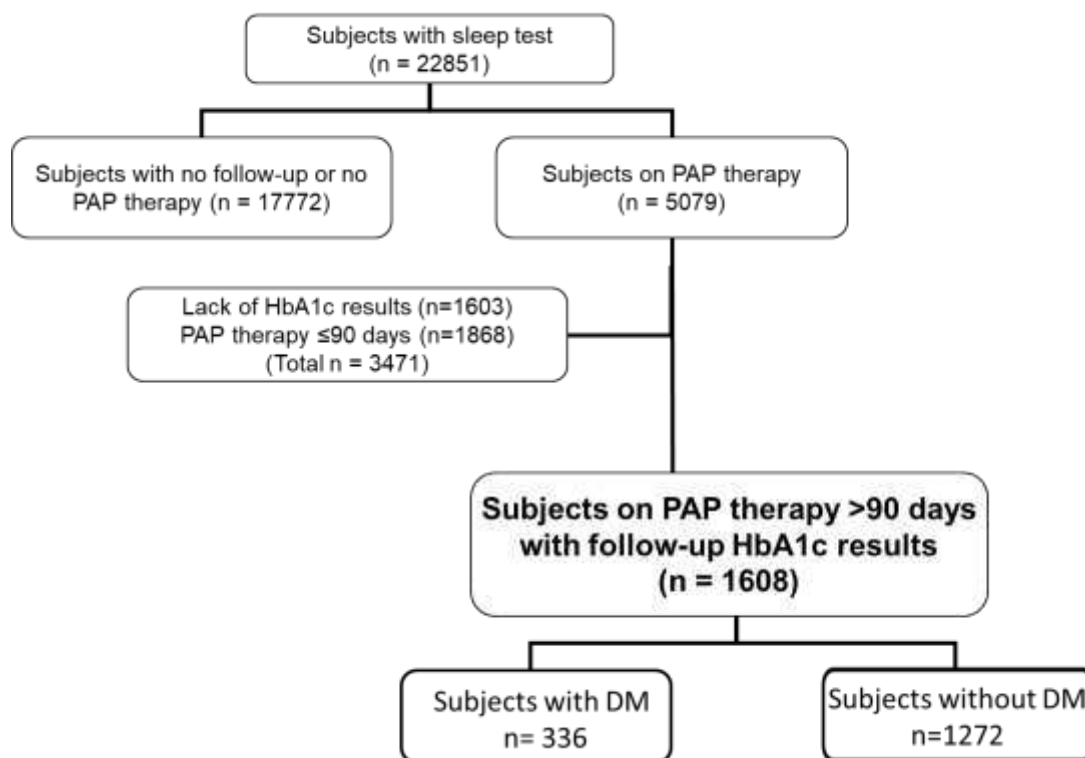


Figure 1. Study flow chart PAP, positive airway pressure

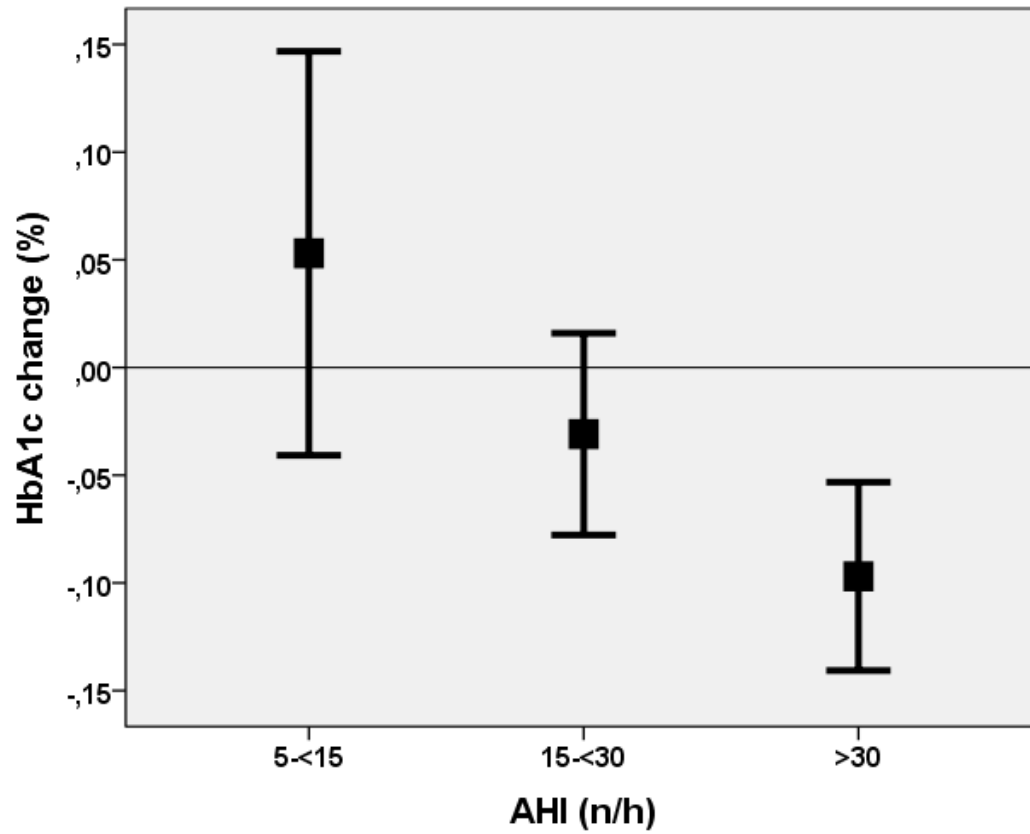


Figure 2. Change in HbA1c levels according to OSA severity (between groups, $p=0.005$)

AHI, apnea-hypopnea index; OSA, obstructive sleep apnea

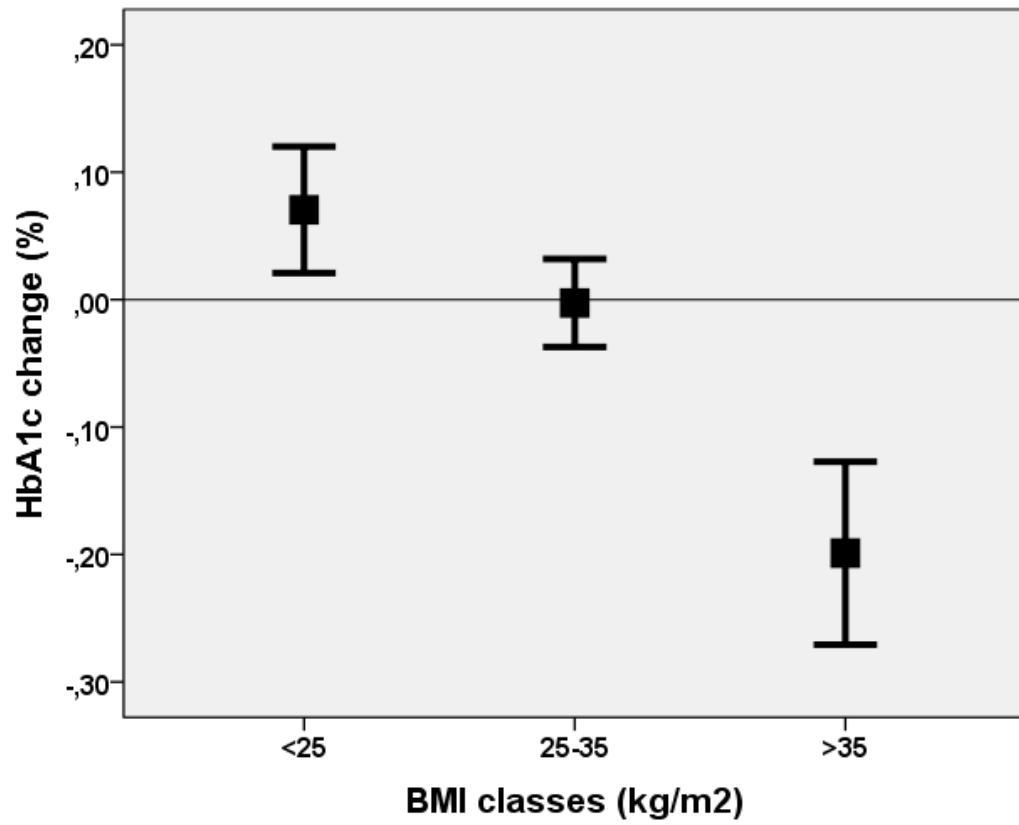


Figure 3. Change in HbA1c levels according to BMI classes (between groups, $p < 0.001$)

BMI, body mass index

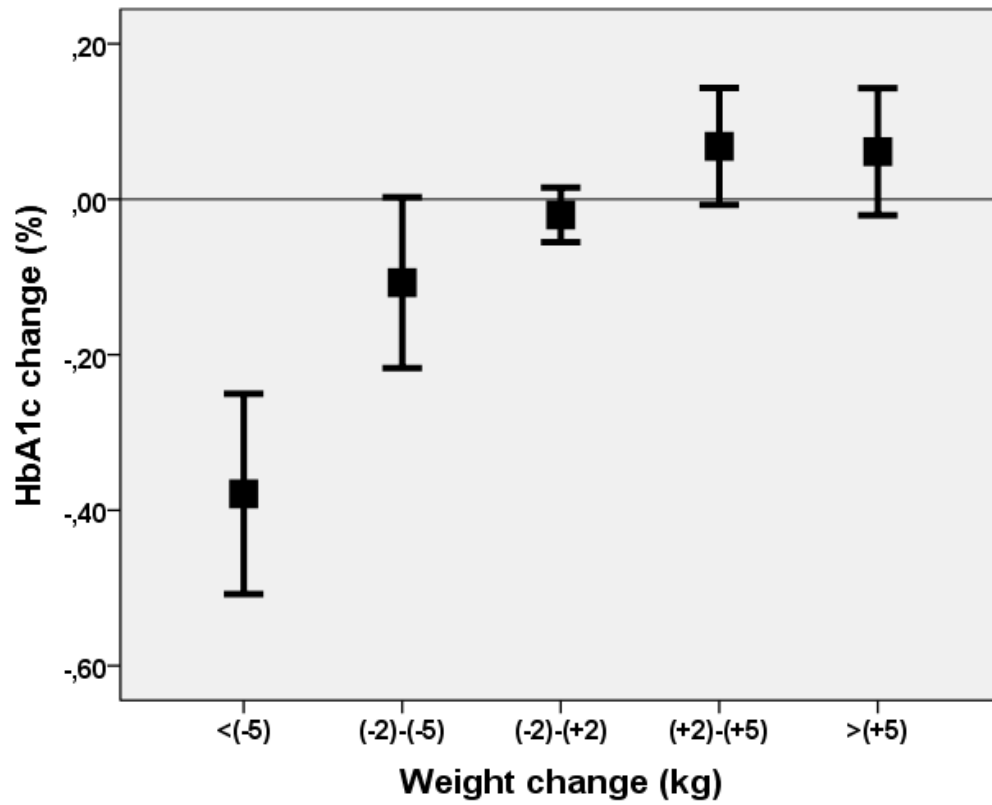


Figure 4. Change in HbA1c levels according to weight reduction (between groups, $p < 0.001$)

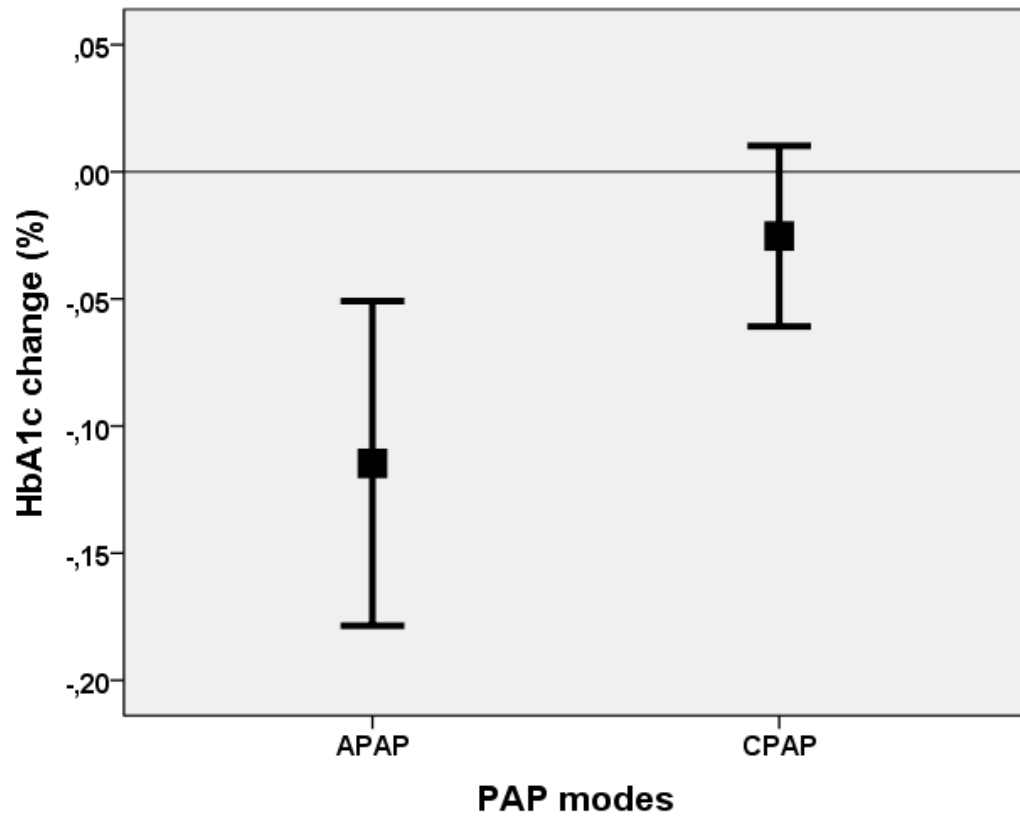


Figure 5. Change in HbA1c according to PAP devices (p=0.030)

APAP, auto-adjusting positive airway pressure; CPAP, continuous positive airway pressure

REFERANCES

1. Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013; 177: 1006-1014.
2. Lattimore JD, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. *J Am Coll Cardiol* 2003; 41: 1429-1437.
3. Schlatzer C, Schwarz EI, Kohler M. The effect of continuous positive airway pressure on metabolic variables in patients with obstructive sleep apnoea. *Chron Respir Dis* 2014; 11: 41-52.
4. Pamidi S, Tasali E. Obstructive sleep apnea and type 2 diabetes: is there a link? *Front Neurol* 2012; 3: 126.
5. Chakhtoura M, Azar ST. Continuous positive airway pressure and type 2 diabetes mellitus. *Diabetes Metab Syndr* 2012; 6: 176-179.
6. Yang D, Liu Z, Yang H, Luo Q. Effects of continuous positive airway pressure on glycemic control and insulin resistance in patients with obstructive sleep apnea: a meta-analysis. *Sleep Breath* 2013; 17: 33-38.
7. Jullian-Desayes I, Joyeux-Faure M, Tamisier R, Launois S, Borel AL, Levy P, Pepin JL. Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. *Sleep Med Rev* 2015; 21: 23-38.
8. Hedner J, Grote L, Bonsignore M, McNicholas W, Lavie P, Parati G, Sliwinski P, Barbé F, De Backer W, Escourrou P, Fietze I, Kvamme JA, Lombardi C, Marrone O, Masa JF, Montserrat JM, Penzel T, Pretl M, Riha R, Rodenstein D, Saaresranta T, Schulz R, Tkacova R, Varoneckas G, Vitols A, Vrints H, Zielinski J. The European Sleep Apnoea Database (ESADA): report from 22 European sleep laboratories. *Eur Respir J* 2011; 38: 635-642.
9. Escourrou P, Grote L, Penzel T, Mcnicholas WT, Verbraecken J, Tkacova R, Riha RL, Hedner J; ESADA Study Group. The diagnostic method has a strong influence on classification of obstructive sleep apnea. *J Sleep Res.* 2015; 24: 730-738.
10. Standards of Practice Committee of the American Sleep Disorders Association. Practice parameters for the use of portable recording in the assessment of obstructive sleep apnea. *Sleep* 1994; 17: 372-377.
11. Iber C, Ancoli-Israeli S, Chesson A, Quan S. The AASM Manual for the Scoring Of Sleep and Associated Events: Rules, Terminology And Technical Specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine, 2007.
12. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540-545.

13. Grote L, Hedner J, Grunstein R, Kraiczi H. Therapy with nCPAP: incomplete elimination of sleep related breathing disorder. *Eur Respir J* 2000; 16: 921-927.
14. Kent BD, Grote L, Bonsignore MR, Saaresranta T, Verbraecken J, Lévy P, Sliwinski P, Tkacova R, Kvamme JA, Fietze I, Hedner J, McNicholas WT; European Sleep Apnoea Database collaborators. Sleep apnoea severity independently predicts glycaemic health in nondiabetic subjects: the ESADA study. *Eur Respir J* 2014; 44: 130-139
15. Kent BD, Grote L, Ryan S, Pépin JL, Bonsignore MR, Tkacova R, Saaresranta T, Verbraecken J, Lévy P, Hedner J, McNicholas WT. Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. *Chest* 2014; 146: 982-990.
16. Malik JA, Masoodi SR, Shoib S. Obstructive sleep apnea in type 2 diabetes and impact of continuous positive airway pressure therapy on glycemic control. *Indian J Endocrinol Metab* 2017; 21: 106-112.
17. Martínez-Cerón E, Barquiel B, Bezos AM, Casitas R, Galera R, García-Benito C, Hernanz A, Alonso-Fernández A, Garcia-Rio F. Effect of continuous positive airway pressure on glycemic control in patients with obstructive sleep apnea and type 2 diabetes. A randomized clinical trial. *Am J Respir Crit Care Med* 2016; 194: 476-485.
18. Shaw JE, Punjabi NM, Naughton MT, Willes L, Bergenstal RM, Cistulli PA, Fulcher GR, Richards GN, Zimmet PZ. The effect of treatment of obstructive sleep apnea on glycemic control in type 2 diabetes. *Am J Respir Crit Care Med* 2016; 193: 486-492.
19. Sophie D West, Debby J Nicoll, Tara M Wallace, David R Matthews, John R Stradling. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. *Thorax* 2007; 62: 969-974.
20. Jullian-Desayes I, Joyeux-Faure M, Tamisier R, Launois S, Borel AL, Levy P, Pepin JL. Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. *Sleep Med Rev* 2015; 21: 23-38.
21. Pamidi S, Wroblewski K, Stepien M, Sharif-Sidi K, Kilkus J, Whitmore H, Tasali E. Eight hours of nightly continuous positive airway pressure treatment of obstructive sleep apnea improves glucose metabolism in patients with prediabetes. A randomized controlled trial. *Am J Respir Crit Care Med* 2015; 192: 96-105.
22. Salord N, Fortuna AM, Monasterio C, Gasa M, Pérez A, Bonsignore MR, Vilarrasa N, Montserrat JM, Mayos M. A randomized controlled trial of continuous positive airway pressure on glucose tolerance in obese patients with obstructive sleep apnea. *Sleep* 2016; 39: 35-41.
23. Basoglu OK, Zou D, Tasbakan MS, Hedner J, Ryan S, Verbraecken J, Escourrou P, Antalainen U, Kvamme JA, Bonsignore MR, Schiza S, Grote L; ESADA Study Group.

Change in weight and central obesity by positive airway pressure treatment in obstructive sleep apnea patients: longitudinal data from the ESADA cohort. *J Sleep Res.* 2018 Dec;27(6):e12705.

24. Chirinos JA, Gurubhagavatula I, Teff K. CPAP, weight loss, or both for obstructive sleep apnea. *N Engl J Med* 2014; 370: 2265-2275.
25. Spiesshoefer J, Aries J, Giannoni A, Emdin M, Fox H, Boentert M, Bitter T, Oldenburg O. APAP therapy does not improve impaired sleep quality and sympatho-vagal balance: a randomized trial in patients with obstructive sleep apnea and systolic heart failure. *Sleep Breath.* 2019 Jun 25. doi: 10.1007/s11325-019-01868-6.
26. Pépin JL, Tamisier R, Baguet JP, Lepaulle B, Arbib F, Arnol N, Timsit JF, Lévy P. Fixed-pressure CPAP versus auto-adjusting CPAP: comparison of efficacy on blood pressure in obstructive sleep apnoea, a randomised clinical trial. *Thorax.* 2016 Aug;71(8):726-33.
27. Marrone O, Cibella F, Pépin JL, Grote L, Verbraecken J, Saaresranta T, Kvamme JA, Basoglu OK, Lombardi C, McNicholas WT, Hedner J, Bonsignore MR; ESADA Network. Fixed ut not autoadjusting positive airway pressure attenuates the time-dependent decline in glomerular filtration rate in patients with OSA. *Chest.* 2018 Aug;154(2):326-334.