SCIENTIFIC INVESTIGATIONS

VAMONOS (Veterans Affairs' Metabolism, Obstructed and Non-Obstructed Sleep) Study: Effects of CPAP Therapy on Glucose Metabolism in Patients with Obstructive Sleep Apnea

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Study Objectives: Obstructive sleep apnea (OSA) and type 2 diabetes mellitus (T2DM) are prevalent disorders that pose increased risk of cardiovascular disease and death. The objective of this study was to clarify if continuous positive airway pressure (CPAP) therapy for OSA affects T2DM control and emergence.

Methods: Point-of-care, comparative effectiveness study; cross-sectional and longitudinal analyses.

Results: Our cohort included 928 consecutive patients; 13% were women; 36% were Caucasians and 61% African-Americans. OSA was diagnosed in approximately 738 patients and CPAP was initiated in 718 patients; median duration of therapy was 5 mo (25% to 75% interquartile range [IQR] 3–14). Patients with OSA used CPAP therapy for a median duration of 4.8 h, 34.5% of the nights. Adherence to CPAP was prespecified as follows: good (≥ 70% nights and ≥ 4 h/night), excellent (≥ 80% nights and ≥ 6 h/night) or outstanding (≥ 90% of nights and 8 h/night). Based on objective data, good, excellent, and outstanding compliance were found in only 30%, 20%, and 6%, respectively. Three percent of subjects without CPAP follow-up and less than 4% of those nonadherent to CPAP therapy (based on the established criteria) developed incident T2DM. Incident T2DM developed in only 0.8% of those with good compliance and in none (0%) of those in the excellent and outstanding groups. During follow-up, median weight change was +0.3 kg (IQR −1.8 to 2.7).

Conclusions: We found that an outstanding compliance to CPAP reduced fasting blood glucose in patients with OSA. Longitudinally, higher levels of therapeutic adherence may affect the rate of incident impaired fasting glucose, prediabetes, and T2DM, despite the observed weight gains.

Commentary: A commentary on this article appears in this issue on page 365.

Keywords: CPAP therapy, diabetes, obstructive sleep apnea, prediabetes, sleep apnea

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INTRODUCTION

Obstructive sleep apnea (OSA) is the one of the most common sleep disorders, yet still significantly underdiagnosed. Current prevalence estimates of moderate to severe OSA (i.e., apnea-hypopnea index [AHI] ≥ 15 events/h) are 10% among 30- to 49-y-old men, 17% in 50- to 70-y-old men, 3% among 30- to 49-y-old women and 9% in 50- to 70-y-old women. These prevalence rates increased by 14% to 55% over the past two decades, depending on the subgroup studied.[1] These epidemiologic changes are strikingly similar to the obesity trends in the general population.[2] Similarly, the prevalence of type 2 diabetes mellitus (T2DM), a condition linked intimately to obesity, has been increasing alarmingly, to more than 8% of the population.[3] Prediabetes is considered an intermediate state between normal glucose metabolism and T2DM, as T2DM develops in approximately 70% of patients.[4] It has been estimated that almost 50% of men and 40% of women of age 50–64 y have prediabetes.[5] Prediabetes is characterized by insulin resistance and glucose intolerance. Prediabetes is defined as fasting blood glucose (FBG) between 100 and 125 mg/dL (also called impaired

fasting glucose, IFG), or a 2-h plasma glucose between 140 and 199 mg/dL after a 75-g oral glucose load or a glycated hemoglobin (hemoglobin A1c, HbA1c) between 5.7% and 6.4%.

In the triangle delineated by obesity, OSA, and T2DM, there are complex bidirectional relationships. As such, obesity is a major risk factor for OSA, but an OSA to obesity directionality

has also been posited. If the connections between obesity and T2DM are well established, there are data showing that OSA and diabetes are also interconnected, both mediated and independent of obesity. Pathophysiologically, increased adiposity, intermittent hypoxia, enhanced sympathetic activity, increased catecholamines and cortisol levels, suppressed slow wave sleep, and sleep fragmentation may all contribute to a certain extent to the development of diabetes mellitus in patients with OSA.

Multiple clinic-based and community studies showed an association between OSA and insulin resistance, IFG, impaired glucose tolerance (IGT), or overt T2DM.[6–10] Despite this relationship, treatment of OSA with continuous positive airway pressure (CPAP) has shown so far mixed results in improving glucose metabolism.[11–13] Several observational studies found that CPAP therapy may improve insulin resistance[14,15] or hemoglobin A1c,[16] whereas others failed to identify significant benefits.[17,18] There were only a handful of published randomized controlled trials evaluating this relationship and their results are also divergent: several studies[12,19] found no changes in hemoglobin glycation or insulin sensitivity after 1–6 mo of CPAP therapy, whereas others found insulin sensitivity improved after 2–6 mo of therapy.[20]

Several meta-analyses have been published in recent years[21,22] assessed the effects of CPAP therapy in studies that used the homeostasis model assessment of insulin resistance (HOMA-IR). In one of them,[21] authors found that CPAP treatment did not significantly change FBG values, but improved HOMA-IR, yet this finding was seen only in patients without T2DM. Iftikhar et al.,[22] looking at pooled data from six studies that evaluated the effects of CPAP only in patients without diabetes, also found a favorable effect of CPAP therapy on insulin resistance in patients with OSA and no diabetes. While the effect size was modest, it was not insignificant, prompting the authors to recommend further studies, involving a larger number of patients and longer treatment periods to clarify the effects of CPAP on insulin resistance.

Since then, a few more controlled randomized studies have been published, but the results have been largely discordant.[23–25] Potential confounders in the available trials are: size of the studies (generally small), patients enrolled (obese or not, normal or dysglycemic), type and duration of treatment, and the actual monitoring of the therapeutic adherence.[26] In order to elucidate some of these discrepancies and to assess these effects in a real-world patient population, we initiated a large, non-randomized, point-of-care, comparative effectiveness study, aimed at evaluating cross-sectionally and longitudinally the effects of CPAP therapy on various metabolic parameters in OSA patients, with and without T2DM. Given that prior studies showed that CPAP usage at higher intensity, i.e., more than the traditional 70% of the nights and more than 4 hours nightly may be more beneficial, we aimed to assess the metabolic effects of CPAP used by more stringent adherence criteria.

METHODS

Patient Assessments

Patient data were collected from Veterans Affairs' electronic medical record system (available since 1991). This is one of the first analyses of the VAMONOS (Veterans Affairs' Metabolism, Obstructed and Non-Obstructed Sleep) study cohort, which is a patient population that we assess periodically for therapeutic adherence, effectiveness, as well as natural history of sleep and associated metabolic conditions. We performed first a retrospective analysis on all (new and established) consecutive patients seen in Atlanta VA Sleep Medicine Clinic by three different providers between 10/1/2012–9/30/2013 (n = 928). The database was created 1 y after the last patient had his sleep clinic evaluation (retrospective component). The subsequent assessment was approximately 1 y later (prospective component). At each visit, height, weight, neck and waist circumference were measured and recorded; body mass index (BMI) was then calculated. Epworth Sleepiness Scale (ESS) and several other questionnaires were administered at all visits. Medical comorbidities were defined as follows: hypertension was recorded if the diagnosis was in the problem list or antihypertensive medications were prescribed for this indication; diabetes mellitus was documented if the disease was found mentioned in the problem list, a hemoglobin A1c level ≥ 6.5% was identified or any prescription for any anti-diabetic medications was found; dyslipidemia was considered present if a diagnosis of "dyslipidemia," "hyperlipidemia" or "hypertriglyceridemia" was found in the problem list or if the patient was on lipid-modifying agents. Coronary artery disease was recorded as present if "angina," "myocardial infarction" or "coronary artery disease" was identified in the problem list or the results of a coronary angiogram were available. Death, incident diabetes and prediabetes were also ascertained from the medical records during the follow-up.

Assessment of Sleep-Disordered Breathing and Adherence to CPAP Therapy

Patients underwent sleep studies as considered clinically indicated and ordered by the respective sleep professionals (per protocol, in order to assess the clinical suspicion of OSA, all patients had a Berlin questionnaire administered at baseline). Sleep testing consisted of polysomnography (PSG) studies in all patients (no home sleep testing) in accordance with the American Academy of Sleep Medicine (AASM) professional standards and the protocols and procedures of our sleep center. Monitoring included pulse oximetry; respiratory effort by inductance plethysmography; electromyographic, electrocardiographic, electroencephalographic, and airflow monitoring (by oronasal thermistor and nasal pressure transducer. Respiratory events were defined per standard AASM 2012 criteria[27]: apnea was defined as a reduction in respiratory flow amplitude of ≥ 90% from baseline (for > 10 sec), and hypopnea was defined as a reduction in flow of ≥ 30% from baseline (for > 10 sec), accompanied by either an arousal or an oxygen desaturation of ≥ 3%. Obstructive apneas and hypopneas were defined by aforementioned flow criteria and presence of respiratory effort. In the analysis, all mixed apneas were categorized as central events and all hypopneas were considered by default obstructive. A diagnosis of OSA was made if AHI was ≥ 5; AHI of 5–14.9 defined mild OSA, 15–29.9 moderate OSA, and ≥ 30 severe OSA, which represent standard severity thresholds. The PSG analyses included the number

Figure 1—Study flow chart.
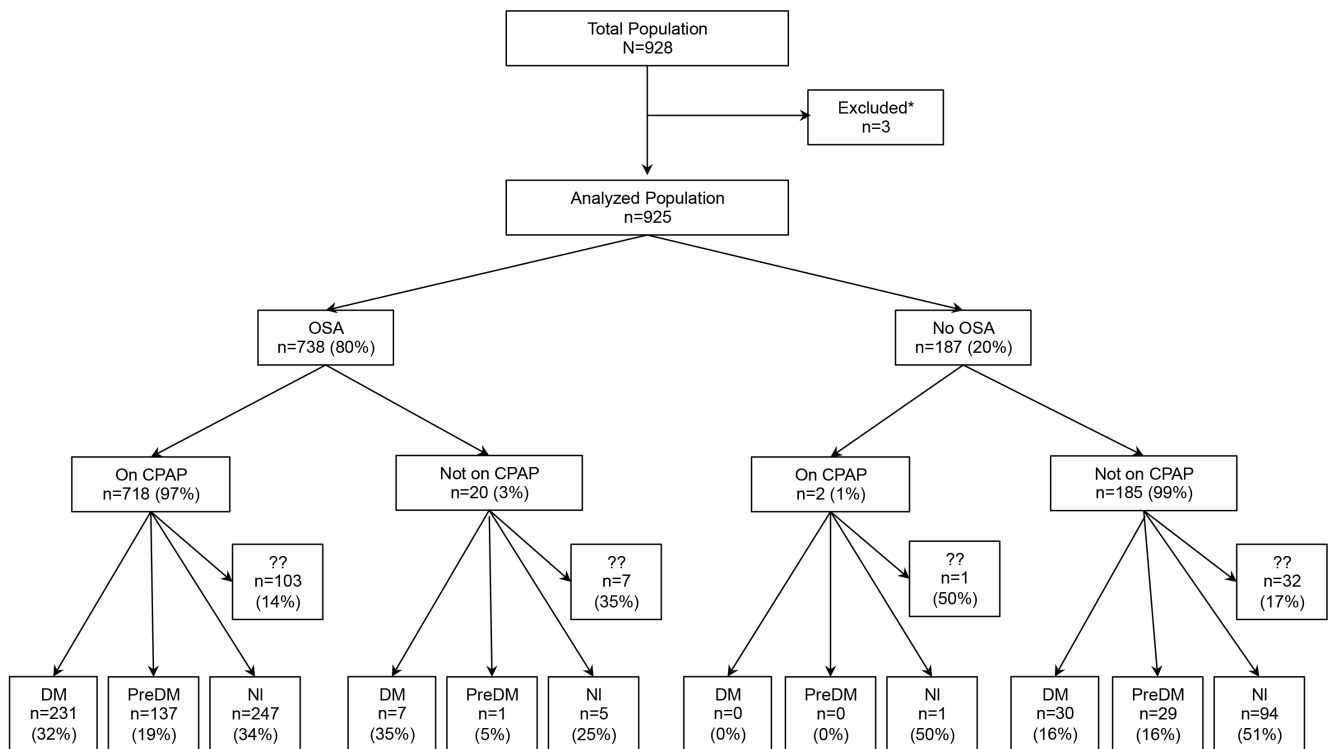
?? = missing both hemoglobin A1C (HbA1c) and fasting blood glucose (FBG), and no antidiabetic medications. Overall only 143 patients (15% of total) were missing values for both HbA1c and FBG. * = patients excluded from analyses due to irreconcilable data. DM = diabetes mellitus, PreDM = prediabetes mellitus (hemoglobin A1c or HbA1c ≥ 6.5%), NI = normal (HbA1c < 5.8%), OSA = obstructive sleep apnea, CPAP = continuous positive airway pressure (included here are all forms of PAP).

of obstructive apneas, central apneas, hypopneas, nadir and mean oxihemoglobin saturation (SpO$_2$), total sleep time, sleep time with SpO$_2$ of ≤ 90%, percentage of sleep time with SpO$_2$ of ≤ 90% (hypoxic burden), oxygen desaturation index, and diagnosis of OSA and/or other sleep disorders.

Based on the PSG findings, positive airway pressure (PAP, in the form of CPAP, bilelvel PAP or other forms, hereafter called for simplicity CPAP) therapy was initiated for all patients with moderate-severe OSA (unless refused) and for mild OSA with significant cardiopulmonary comorbidities or daytime symptoms (**Figure 1**). The majority of patients were started on autoadjustable CPAP therapy (6–18 cm H$_2$O), unless a dedicated titration was ordered and identified an optimal PAP setting. CPAP initiation date was recorded when the device was programmed and issued, and CPAP education was performed by a dedicated technologist in a 1:1 session lasting 30–45 min. At the subsequent visit, CPAP device was interrogated by smart card or "cloud"-based system download and the percentage of nights used, median hours of usage nightly, and fixed, P95/P90 level (in cm H$_2$0, as reported by the device) were recorded. At least 2 mo after CPAP initiation, patients were seen again in clinic; weight, neck girth, waist circumference, and Epworth Sleepiness Scale (ESS) score were reassessed. Adherence to CPAP therapy was assessed by interview (subjectively) and by interrogation of the CPAP device (objectively). Adherence to CPAP therapy was defined as percent of nights used and by the

median number of hours of CPAP usage nightly. Three classification systems of CPAP use were defined *a priori* (**Figure 2**): good (median ≥ 4 h *and* ≥ 70% of nights used), excellent (median ≥ 6 h *and* ≥ 80% of nights used) and outstanding compliance (median ≥ 8 h *and* ≥ 90% of nights used). Those who met these specific criteria were considered adherent (+), whereas those who did not meet the criteria were, for the purpose of these analyses, nonadherent (−).

Laboratory Assessments

Pretreatment and posttreatment metabolic parameters (hemoglobin A1c or HBA1c, fasting blood glucose or FBG, total cholesterol, calculated low-density lipoprotein cholesterol, high-density cholesterol, and triglycerides) immediately before and after at least 2 mo of CPAP therapy were extracted. Prediabetes and diabetes were defined by standard criteria, i.e., HbA1c 5.7% to 6.49%, and ≥ 6.5%, respectively; IFG was defined as FBG level of ≥ 100 and < 126 mg/dL. Any changes in antihypertensive regimen, lipid modifying agents, or diabetes medications were recorded.

Statistical Analysis

Statistical analysis was performed using JMP 13 Pro software (SAS Institute, Cary, NC, USA). Continuous variables were presented as mean and standard deviation (when distribution was normal) or median and 25% to 75% IQR (when

Figure 2—Compliance graph.
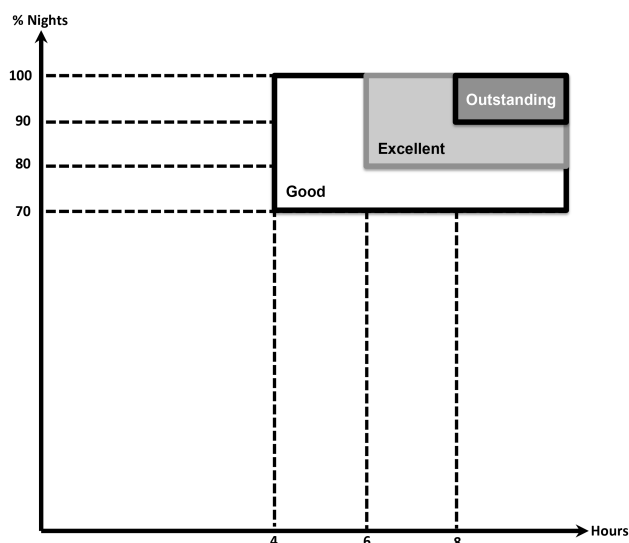
Depiction of % of nights of continuous positive airway pressure (CPAP) usage (on Y axis) versus median hours of CPAP usage (on X axis) and the three compliance categories (good, excellent, and outstanding).

distribution was not normal); Normality of each variable was checked using Q-Q plots and verified for goodness of fit by using Shapiro-Wilk W or Kolmogorov-Smirnov tests, as appropriate. We compared continuous variables between groups using Student t or equivalent tests (e.g., Tukey-Kramer honest significant difference) when variances were similar or Wilcoxon/Kruskal-Wallis rank-sum test for groups with different variances. Tests used to verify that the variances were equal were: O'Brien [0.5], Brown-Forsythe, Levene, Bartlett, and two-sided F test (in all analyses) and adjudicated based on a minimum of three out of five tests concordant for significance and when discordant, giving priority to the first three tests. Baseline categorical characteristics were compared between groups using chi-square and Fisher exact tests (when appropriate). The relationships between different variables and delta HbA1c or delta FBG were determined by Pearson correlation and simple regression analysis using weighted least squares. Various parameters were then included in stepwise multiple linear regression analyses; these models were run to investigate if changes in body mass index (BMI), weight, or other variables had an effect on absolute or delta values for HbA1c and FBG. Colinearity was also evaluated by the variance inflation factor. Logistic regression models were also used to investigate the influence of other variables on incident diabetes, prediabetes, and IFG. Missing data analysis was also performed; the imputation of missing values was accomplished by two different methods in JMP Pro: (1) means method, i.e., using the means of the existing values to replace the missing values; (2) expectation maximization method, which entails several iterations (at first pass the missing values are replaced with the means of the existing values, while at successive iterations, the missing values are replaced with the predicted values using the previous model). A two-sided $p < 0.05$ was considered statistically significant.

Institutional review committee approvals were obtained for this project (Emory University IRB# 00049576, Atlanta VA R&D# 2610, VA# 002); no informed consent was necessary. This study is an investigator-initiated project without a specific source of funding at the time of this publication.

Preliminary results of this analysis have been communicated in an oral presentation at the 2015 CHEST (American College of Chest Physicians) meeting, in Montreal, Canada, October 2015.[28]

RESULTS

Demographic Data

The cohort included 928 consecutive patients seen in sleep clinics by three healthcare professionals (KMC, MMC, and OCI). Three subjects were excluded from analyses due to documentation errors or irreconcilable data. **Figure 1** shows the study flow chart, detailing the main diagnoses, i.e., OSA versus no OSA, on CPAP therapy or not, and the glucose metabolism status at baseline (normal, prediabetes, or diabetes mellitus). The diagnosis of OSA was already established at baseline in 39% of patients (due to a study ordered and performed before the Sleep Clinic visit 1 of the inclusion period) or the baseline visit identified a high clinical probability of sleep-disordered breathing, and hence a diagnostic PSG was ordered. We identified 143 subjects who did not have HbA1c or FBG available in the computerized system prior to CPAP initiation, did not carry a diagnosis of diabetes mellitus or prediabetes, and were not on any antidiabetic medications. In **Figure 1**, we classified these subjects in "unknown status," yet the majority of them were likely in the normal category, as only a very small fraction of patients would have had their entire care for the aforementioned conditions outside our system.

Among the 925 subjects, 803 (87%) were males and 122 (13%) were females; 328 were self-reported as Caucasians or whites (36%) and 560 as African-Americans or blacks (61%, **Table 1**). At baseline, 64% were obese (BMI ≥ 30), 29% were overweight (25 ≤ BMI < 30) and 7% had normal weight (BMI < 25). Men were heavier than women (median weight 103 versus 87 kg, respectively, p < 0.001), but the overall BMI distribution was similar (median BMI was 32 kg/m² for both sexes, p = 0.95). Obesity rates were also similar in the two groups (64% and 67% in men and women, respectively, p = 0.76). Neck and abdominal circumferences were significantly higher in men versus women (p < 0.001). Among the 738 patients with OSA, 521 (71%) had excessive daytime sleepiness (EDS, i.e., ESS > 10), 206 (28%) had no EDS (ESS < 10) and 11 subjects' (1%) ESS score was unknown. Among patients without OSA, 131 (70%) had EDS, 51 (27%) did not have EDS and 5 (3%) did not have an ESS score. In those with OSA and on CPAP therapy, 72% had EDS (similar rates in different severity groups), while among patients with untreated previously diagnosed OSA only 57% had EDS (likely explaining why they were not placed on therapy). Among patients with OSA, 50% of men and 34% of women had moderate-severe OSA.

Table 1—Initial characteristics of the cohort (n = 928).

Age (y)	Median 54.8; IQR 63.0–46.2; n = 925
Sex	Males 803 (86%), Females 122 (13%); n = 925
Race	Caucasian or White 328 (36%), African American or Black 560 (61%), Hispanic 7 (0.007%), Other 10 (0.01%); n = 905
Weight (kg)	Mean 104.2; SD 22.7; n = 883
Height (cm)	Median 177.8; IQR 172.7–182.9; n = 898
Body mass index (BMI, kg/m²)	Median 31.8; IQR 28.4–36.6; n = 883
Neck circumference (cm)	Mean 43.2; SD 4.4; n = 866
Abdominal circumference (cm)	Mean 110; SD 16.2; n = 696
Smoking status	Current 195 (21%), Ex-smoker 223 (24%), Never smoker 501 (54%); n = 919
Obesity	609 (65%); n = 883
Diabetes mellitus	258 (28%); on therapy: 214 (23%); n = 925
Dyslipidemia	485 (52%); on therapy: 399 (43%); n = 925
Hypertension	587 (63%); on therapy: 528 (57%); n = 925
Coronary artery disease	99 (11%); n = 925

Normally distributed variables are reported as mean and standard deviation, whereas non-gaussian distributed parameters are reported as median and interquartile range. BMI = body mass index, IQR = 25th–75th interquartile range, n = number of patients for whom we had data available for the respective analyses, SD = standard deviation.

Approximately 28% of subjects in the cohort had a diagnosis of diabetes mellitus, 52% dyslipidemia, 63% hypertension, and 11% had coronary artery disease. Among subjects with T2DM, 83% were on anti-diabetic medications; 23% were on insulin only, and 23% were on insulin and a second agent.

Polysomonographic Parameters

Median total sleep time was 327 min (IQR 268.75–366; range 21.5–519) and median sleep efficiency was 80.7% (IQR: 69–88.2, range: 9.1–100). Median AHI was 11 (IQR 5.5–20.7, range: 0–146); median central apnea index was 0.13 (IQR 0–0.64, range: 0–34.2); median obstructive apnea index was 2.1 (0.5–6.5, range: 0–97.5); median hypopnea index was 6.9 events/h (IQR 2.7–12.6, range 0–75.6). Median nadir oxyhemoglobin saturation was 84% (IQR 79–88, range: 31–96), whereas the median of the mean oxyhemoglobin saturation was 94% (IQR 92–96, range: 65–100); median time with an oxygen saturation < 90% was 6.8 min (IQR 0.6–39.6, range: 0–415.9), whereas median hypoxic burden was 2.2% (IQR 0.2–15, range: 0–100).

Patient Assessments

After clinical and polysomnographic evaluation, 738 patients (80%) received a diagnosis of OSA; 52% of them had mild, 30% moderate, and 18% severe OSA. Among these subjects, 718 (78%) were started on CPAP therapy. Patients were followed between the Sleep Clinic visit 1 and the CPAP follow-up for a median of 9 mo (IQR 5–12). Between the date of PSG and the follow-up CPAP clinic visit, approximately 2 mo (median) passed (with an IQR of 1–5 mo). Over the period of follow-up (i.e., between the initial and follow-up clinic visits), median weight change was +0.3 kg (IQR −1.8 to 2.7), which corresponds to a median increase in BMI of 0.1 kg/m² (IQR −0.6 to 0.8) (p < 0.05 for both).

CPAP Therapy

CPAP therapy was initiated for all patients with moderate-severe OSA who accepted it (n = 277), for mild OSA with significant cardiopulmonary comorbidity or daytime symptoms (n = 296), and for subjects with OSA of unknown severity (PSG studies not available) *and* EDS (ESS score > 10) or other comorbidities (n = 145). In addition, two patients from the non-OSA group, with a diagnosis of upper airway resistance syndrome and daytime symptoms were started on CPAP. After discussions with their healthcare professional, 11 patients with OSA were started on other therapeutic modalities (i.e., not positive airway pressure). CPAP therapy was not instituted in 20 patients: 4 patients with unknown OSA severity, 7 subjects with moderate-severe OSA who refused or did not tolerate CPAP during the initial setup, 3 subjects with mild OSA and no EDS (ESS ≤ 10), and 6 patients with mild OSA and EDS. Because this was not a randomized study with specific allocations, patients received therapy in accordance to the aforementioned criteria and the discussion with their healthcare professional.

Overall, CPAP therapy was initiated in 720 of the cohort patients (78%); 718 for OSA and 2 for upper airway resistance syndrome. The PAP modalities used were: autoadjustable CPAP (51% of cases), fixed CPAP (33% of patients), fixed bilevel PAP (9%), autoadjustable bilevel PAP (5%), servoventilation (< 1%) or volume-assured pressure support ventilation (< 1%).

Median p95/p90 or fixed CPAP setting for patients with OSA was 11 cm H_2O (IQR 9.4–13.1, range 5–20.5), used for a median of 4.8 h (IQR 2.8–6.5, range 0–10.8; 40th percentile: 4.0; 60th percentile: 6.0), and a median of 34.5% (IQR 5–79.1, range 0–100, 71st percentile: 70, 78th percentile: 80) of the nights. Median duration of CPAP follow-up was 5 mo (IQR 3–14, range: 0–248). Median residual AHI was 2, with only 5% of patients having values more than 10 events/h.

Good (+) CPAP compliance, i.e., median hours ≥ 4 *and* % of nights ≥ 70, was found in 174 (30%) of patients, whereas 414 did not meet criteria for good compliance (−) [missing data: n = 337]. Excellent (+) CPAP compliance, i.e., median

Table 2—Metabolic parameters in obstructive sleep apnea versus controls, and mild versus moderate-severe obstructive sleep apnea.

Baseline Characteristics (n = 925)	No OSA (n = 187)	OSA (n = 738)	p	Mild OSA (n = 310)	Moderate or Severe OSA (n = 286)	p
Age (y)	48.6	53.9	< 0.001*	52.8	55.9	0.0018*#
Weight (kg)	91.3	107.5	< 0.001*	102.4	112.2	< 0.0001*#
Body mass index (BMI, kg/m^2)	29.6	33.9	< 0.001*#	32.5	35.3	< 0.001*#
Fasting blood glucose (FBG, mg/dL)	99.1	107.1	0.001*#	104.5	111.2	0.22#
Hemoglobin A1c (%)	6.1	6.4	0.007*	6.23	6.71	0.0005*#
Total cholesterol (mg/dL)	179.1	178.3	0.82	180.4	174.8	0.11
LDL cholesterol (mg/dL)	110.0	107.7	0.47	110.1	104.5	0.08
HDL cholesterol (mg/dL)	45.9	42.6	0.0032*	45.9	42.6	0.0032*
Ratio total cholesterol/HDL cholesterol	4.2	4.4	0.0248*	4.4	4.5	0.11#
Triglycerides (mg/dL)	121.2	145.4	0.01*	142.8	149.5	0.50
Neck circumference (cm)	40.4	43.9	< 0.0001*#	42.6	45.0	< 0.0001*#
Abdominal circumference (cm)	99.9	112.9	< 0.0001*#	108.7	117.5	< 0.0001*
Epworth Sleepiness Scale (ESS, 0–24)	14.0	13.9	0.90	14.0	13.9	0.65

For groups with similar variances, Tukey-Kramer honest significant difference tests were performed. # = Wilcoxon/Kruskal-Wallis test for groups with unequal variances, * = statistically significant. HDL = high density lipoprotein, LDL = low density lipoprotein, n = the number of patients in entire cohort and in each group, OSA = obstructive sleep apnea.

Table 3—Main glucose metabolism variables in patients with and without obstructive sleep apnea.

Variable	No OSA			OSA			No OSA vs. OSA (p statistic)	
	pre	post	p	pre	post	p	pre	post
HbA1c	6.05	6.17	0.40	6.43	6.64	0.0002*	0.001*	0.005*
FBG	99.10	101.90	0.44	107.20	112.80	0.01*	0.007*	0.018*#

* = statistically significant. For groups with similar variances, Tukey-Kramer hones significant difference tests were performed. # = Wilcoxon/Kruskal-Wallis test for groups with unequal variances. FBG = fasting blood glucose, HbA1c = hemoglobin A1c, OSA = obstructive sleep apnea.

hours ≥ 6 *and* % of nights ≥ 80, was found in 118 (20%) of patients, whereas 474 did not meet criteria for excellent compliance (−) [missing data: n = 333]. Outstanding (+) CPAP compliance, i.e., median hours ≥ 8 *and* % of nights ≥ 90, was found in 36 (6%) of patients, while 557 did not meet criteria for outstanding compliance (−) [missing data: n = 332] (**Figure 2**).

Patients with mild OSA used CPAP therapy 34% of nights, with a median of 4.3 h; those with moderate-severe OSA used it 44% of the nights and 4.6 h nightly (differences nonsignificant for the number of hours—p = 0.16 by Tukey-Kramer honest significant difference test, and significant for the percent of nights—p = 0.007 by Wilcoxon/Kruskal-Wallis test). As expected, individuals with more severe sleep-disordered breathing had better adherence to therapy. As such, those with mild OSA met criteria for (+) good, (+) excellent or (+) outstanding compliance in 23%, 13%, and 4.4%, respectively. Patients with moderate-severe OSA met the same criteria in 32%, 22%, and 4.6%, respectively (differences between groups significant only in good and excellent compliance categories, p < 0.04).

There was an interaction between age of the patient and the CPAP compliance: younger patients and those with mild (versus moderate-severe) OSA had poorer compliance (p < 0.004). Not surprisingly, OSA severity correlated directly with the age and the weight of the patients (**Table 2**).

Glucose Metabolism

Tables 2 and **3** show baseline metabolic variables in patients without OSA versus OSA, mild versus moderate-severe OSA. Of note, FBG and HbA1c were significantly higher in OSA patients versus non-OSA subjects, both at baseline and at follow-up. While in patients without OSA, FBG and HbA1c did not change significantly over the period of follow-up, they both increased significantly in those with OSA. As seen in **Table 4**, this happened in parallel with increases in body weight and BMI, in most of the compliance groups or categories.

At baseline, mean HbA1c was 6.32% in African-Americans and 6.39% in Caucasians (p = 0.93). Similarly, mean FBG was 104 mg/dL in African Americans and 108 mg/dL in Caucasians (p = 0.55), despite similar mean weights of 104 kg at baseline. These findings alleviated the potential confounding posed by the known fact that HbA1c may be slightly higher in African Americans versus Caucasians for similar blood glucose levels, especially as standard diagnoses of prediabetes and T2DM entail fixed thresholds of 5.7% to 6.4% and 6.5%, respectively.

The analyses of post-CPAP minus pre-CPAP values (delta) for FBG and HbA1c in adherent (+) versus nonadherent (−) groups using good, excellent, and outstanding compliance criteria are illustrated in **Figure 3** and **Table 4**. As shown, we found a (nonsignificant) increase in weight in the adherent (+) versus the nonadherent (−) groups for good, excellent,

Figure 3—Change over time (delta) in fasting blood glucose (FBG, mg/dL), hemoglobin A1c (HbA1c, %) and weight (kg) in various compliance groups.
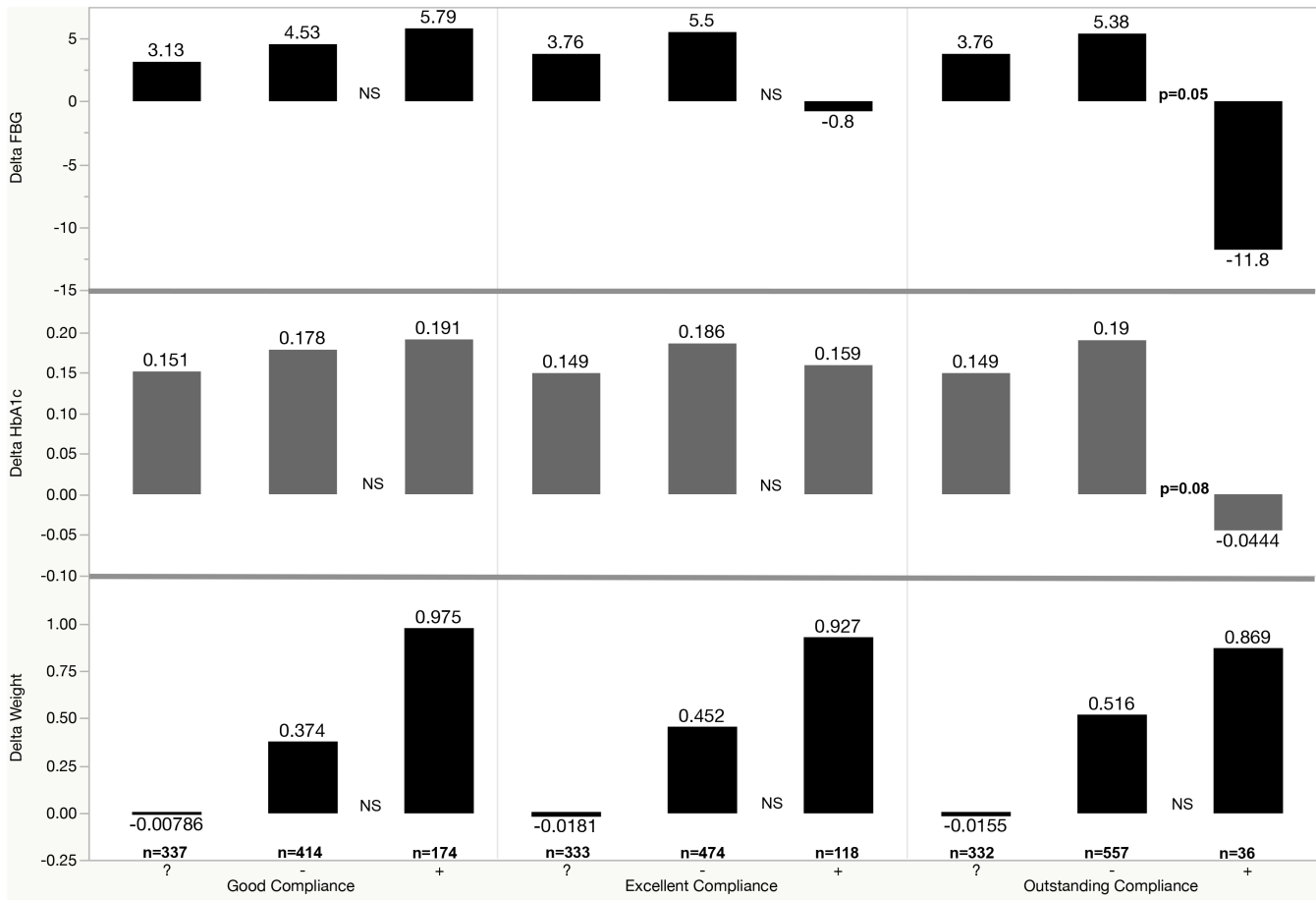
On the X axis, we illustrated the following groups: (?) = no continuous positive airway pressure follow-up, (−) = patients who do not meet the respective compliance category criteria, (+) = patients who meet the respective compliance category criteria. For good compliance criteria (≥ 70% nights and ≥ 4 h), there were 337 subjects in group (?), 414 in group (−) and 174 in group (+). For excellent compliance criteria (≥ 80% nights and ≥ 6 h), there were 333 subjects in group (?), 474 in group (−) and 118 in group (+). For outstanding compliance criteria (≥ 90% nights and ≥ 8 h), there were 332 subjects in group (?), 557 in group (−) and 36 in group (+). NS = not significant (statistically).

Table 4—Glucose metabolism parameters, weight, and body mass index in various groups of compliance.

Variables	Time	Good Compliance			Excellent Compliance			Outstanding Compliance		
		?	−	+	?	−	+	?	−	+
Weight (kg)	pre	100.00	104.78	111.49	99.97	105.26	112.6	100.00	106.68	106.59
	post	99.23	105.13	111.46	99.2	105.65	112.2	99.28	106.84	106.70
BMI (kg/m²)	pre	31.83	33.17	34.99	31.82	33.29	35.31	31.82	33.66	34.04
	post	31.81	33.24	34.95	31.82	33.38	35.14	31.81	33.67	34.22
FBG (mg/dL)	pre	102.84	106.5	108.91	102.42	106.87	109.71	102.45	107.11	110.58
	post	106.53	112.51	113.72	106.48	113.48	110.25	106.48	113.19	107.50
HbA1c (%)	pre	6.18	6.51	6.35	6.18	6.48	6.39	6.18	6.47	6.39
	post	6.37	6.71	6.54	6.36	6.71	6.5	6.36	6.68	6.44

BMI = body mass index, FBG = fasting blood glucose, HbA1c = hemoglobin A1c, ? = no continuous positive airway pressure (CPAP) follow-up data, (−) = does not meet CPAP compliance criteria, (+) = meets CPAP compliance criteria. Good Compliance = ≥ 70% nights and ≥ 4 h/night, Excellent Compliance = ≥ 80% nights and ≥ 6 h/night, Outstanding Compliance = ≥ 90% nights and ≥ 8 h/night.

or outstanding compliance. Changes in BMI were also higher in the adherent (+) versus non-adherent (−) groups, but also nonsignificant statistically. During the same time, FBG decreased in the (+) excellent category (nonsignificantly) and

Table 5—Delta hemoglobin A1c and fasting blood glucose versus continuous positive airway pressure compliance categories and main racial groups.

Parameter	Race	Good Compliance			Excellent Compliance			Outstanding Compliance		
		−	+	p	−	+	p	−	+	p
Delta HbA1c (%)	C	+0.37	+0.01	0.03*	+0.33	−0.08	0.02*	+0.23	−0.04	0.31
	AA	+0.48	+0.16	0.08	+0.64	+0.17	0.57	+0.02	−	−
	All	+0.19	+0.18	0.92	+0.19	+0.16	0.86	+0.19	−0.04	0.08
Delta FBG (mg/dL)	C	+7.38	−0.51	0.32	+8.10	−8.70	0.055	+5.20	−12.50	0.16
	AA	+14.30	+2.86	0.09	+13.27	+4.01	0.31	+5.12	−9.75	0.42
	All	+4.53	+5.79	0.79	+5.50	−0.80	0.28	+5.38	−11.80	0.42

AA = African-Americans, C = Caucasians, Delta = difference post-continuous positive airway pressure (CPAP) minus pre-CPAP values, FBG = fasting blood glucose (mg/dL), HbA1c = hemoglobin A1c (%), (−) = does not meet CPAP compliance criteria, (+) = meets CPAP compliance criteria. Good Compliance = ≥ 70% nights and ≥ 4 h/night, Excellent Compliance = ≥ 80% nights and ≥ 6 h/night, Outstanding Compliance = ≥ 90% nights and ≥ 8 h/night.

Figure 4—Incident impaired fasting glucose.
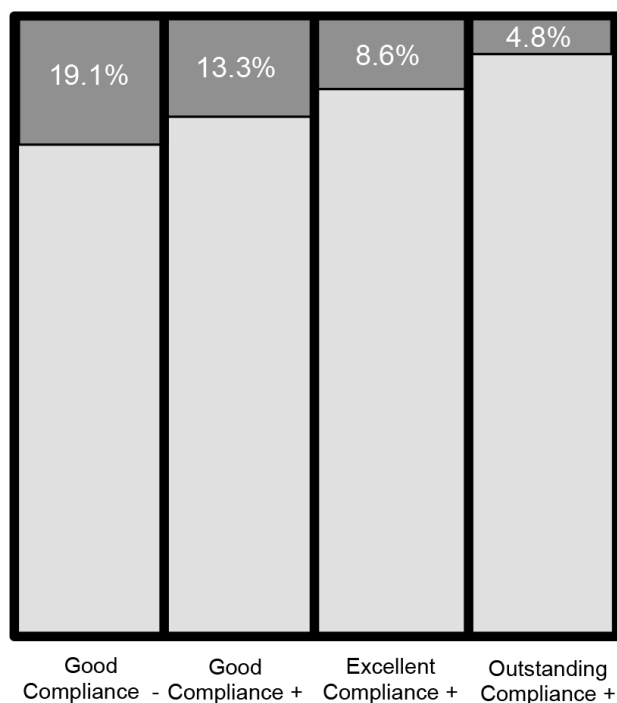
Incident impaired fasting glucose in patients who did not meet criteria for good (−) vs good (+), excellent (+) or outstanding (+) compliance, respectively.

in the (+) outstanding compliance category (p = 0.05). The HbA1c decreased only in the (+) outstanding category, with a value of p = 0.08. In multivariate analyses, delta FBG remained significantly lower in adherent (+) outstanding category, even in models that included delta weight or delta BMI (p < 0.05). Interestingly, when the same parameters were analyzed by different racial groups, we found that delta HbA1c was significantly lower in Caucasians who met criteria for (+) good and (+) excellent compliance (p = 0.03 and p = 0.02, respectively), whereas in African-Americans there was only a trend in the same compliance categories (p = 0.08 and p = 0.057, respectively). **Table 5** illustrates these changes in HbA1c and FBG by race and different compliance categories.

Two parameters were stronger predictors on univariate analyses (baseline neck and abdominal circumferences), but "lost" their significance in multiple regression analyses (data not shown). Several stepwise multiple linear regression models found that changes in BMI, weight, or other variables had no effects on absolute or delta values for HbA1c and FBG. We also assessed for possible confounding from the type of therapy the patients with T2DM received, as well as any changes in anti-diabetic prescriptions over the period of follow-up (28 patients, 3%) and we found no significant result changes.

Lipid Metabolism

During the follow-up, 85 patients (9.1%) had changes in treatment for dyslipidemia; these effects were considered when we analyzed the metabolic parameters before and after CPAP therapy and they did not influence significantly the reported findings. Overall, no significant changes in lipid metabolism parameters were noted after CPAP therapy (data not shown), likely due to the duration of follow-up and/or changes in weight observed.

Incident Diabetes and Prediabetes

Despite the relatively short period of follow-up, we found different rates of new or incident conditions such as new IFG, prediabetes, or diabetes.

Among individuals without T2DM or prediabetes at baseline ("normal" subjects), in approximately 19% of CPAP nonadherent subjects, i.e., with (−) good, (−) excellent, or (−) outstanding compliance IFG developed at follow-up. By contrast, only 15%, 8%, and 5% of those with (+) good, (+) excellent, and (+) outstanding compliance, respectively, had IFG at subsequent testing (**Figure 4**). In the same "normal" group, in 2% of nonadherent individuals diabetes developed at follow-up. By contrast, 0% was the incidence of T2DM in (+) good, (+) excellent, and (+) outstanding compliance categories (again, possibly due to relatively short follow-up).

In patients with prediabetes at baseline, in approximately 15% of the nonadherent subjects, i.e., with (−) good, (−) excellent, or (−) outstanding compliance T2DM developed over time. At follow-up in the adherent categories, i.e., (+) good, (+) excellent and (+) outstanding compliance, diabetes developed in 6%, 0%, and 0%, respectively.

No other variables had an effect on these incident conditions, including delta weight and delta BMI.

All these data show that development of T2DM and prediabetes seems to be mitigated in those who meet criteria for excellent or outstanding compliance.

DISCUSSION

This study on mostly obese and overweight patients with OSA shows that CPAP therapy exerts positive metabolic effects, reducing hemoglobin A1c and fasting glucose, but only in those with excellent or outstanding therapeutic adherence. Similarly, the risk of developing impaired fasting glucose and diabetes was reduced by sustained CPAP therapy. Both these findings were not influenced by the slight increase in BMI or weight over the same period of follow-up.

Sleep apnea and cardiometabolic parameters are interconnected by complex relationships.[11,29,30] Several mechanisms explaining the connection between glucose dysregulation and OSA have been proposed, including increased catecholamines, elevated sympathetic tone, oxidative stress, intermittent hypoxia,[30] elevated cortisol levels, increased inflammatory cytokines, and changes in adipokines.[31,32]

Multiple clinic-based and community studies showed an association between OSA and insulin resistance, IFG, IGT or overt T2DM.[6–10] For example, in a single-center, cross-sectional study of patients with T2DM and HbA1c ≥ 7%, those with intermittent hypoxia had higher HbA1c levels than those without, even after controlling for obesity, age, duration of diabetes, insulin requirement, sleep quality, or depressive mood.[30] In a cross-sectional study of 762 patients undergoing sleep studies for OSA, HbA1c was correlated with the AHI and with the 3% oxygen desaturation index in the untreated group, but not in the treated group. In those with treated T2DM, for unclear reasons, the HbA1c was not associated with the sleep variables.[33] Among 115 patients with T2DM who underwent sleep studies to evaluate the effect of rapid eye movement (REM) versus non-REM sleep on baseline metabolic variables, the authors found a correlation between REM, AHI, and HbA1c, whereas in non-REM sleep this was not the case.[34] This suggests that treating OSA that occurs during REM sleep may have an effect on glycemic control. As such, authors projected that 7 h of CPAP use would be needed to treat 85% of REM sleep. Thus, duration of CPAP use may affect glycemic control by influencing OSA during REM sleep.

Despite this relationship, CPAP therapy has shown so far mixed results in improving glucose metabolism.[11–13,21,22]

Several studies on individuals without diabetes showed no change in glucose metabolism with CPAP.[13,35] In 2013, Yang et al.[21] published a meta-analysis of the glycemic effects of CPAP therapy in patients with OSA. They included only prospective observational studies, in adults with moderate or severe OSA, receiving CPAP therapy for more than 2 w. Studies included were published between 2006 and 2010 and used HOMA-IR, as well as FBG and BMI before and after CPAP. Of the 11 final studies analyzed, 2 studies were in patients with diabetes and 9 trials in patients without T2DM. In one of their conclusions,

Yang et al. found that 3–24 w of CPAP therapy did not improve FBG values in neither groups (i.e., patients with or without diabetes). Additionally, CPAP therapy led to an improvement in HOMR-IR of 0.55 points versus pretreatment in studies on patients without T2DM at baseline (n = 248 patients). In the two studies on diabetic subjects (n = 39), HOMA-IR reduction was not significant. With the addition of a few more studies not included in the previous meta-analyses,[21,36] Iftikhar et al.[22] published in 2015 an updated meta-analysis, that confirmed CPAP therapy has a favorable effect on insulin resistance. The pooled estimates of these trials showed a favorable effect of CPAP therapy for 1–12 w on insulin resistance in patients with OSA and without diabetes.

In a more recent and elegant study on patients with prediabetes, CPAP used for 2 w, 8 h nightly (with actual sleep time < 7 h) versus oral placebo improved glucose metabolism significantly, as assessed by both intravenous and oral glucose tolerance test.[23]

Several observational studies found that CPAP therapy may improve insulin resistance[14,15] or hemoglobin A1c,[16] whereas others failed to identify significant benefits.[17,18,37] To date, there are only a few randomized controlled trials evaluating this relationship and their results are also divergent: several studies[12,19,24] found no changes in hemoglobin glycation or insulin sensitivity after 1–6 mo of CPAP therapy, whereas others found insulin sensitivity improved after 2–6 mo of therapy.[20,25] A double-blind, placebo-controlled trial on 42 men with diabetes and OSA treated with 3 mo of CPAP versus sham showed no change in HbA1c or euglycemic clamp results. It is interesting to note that the CPAP use was on average < 4 h per night in each group.[12] In another study, on 25 patients with diabetes and OSA who were treated with CPAP for 90 days, FBG, HbA1c and continuous glucose monitoring for 72 h were performed at baseline, at 30 days and at 90 days.[16] Postprandial glucose excursions were improved after treatment, and in those with HbA1c > 7%, there was significant HbA1c reduction with treatment. Furthermore, in subjects who used CPAP for more than 4 h nightly, the reduction in HbA1c level was significantly correlated with the number of days of CPAP use. There was no such a correlation in subjects who used CPAP therapy for 4 h per night or less.[16]

Overall, in the existing literature, there is significant heterogeneity in study design, patient selection (patients with diabetes, prediabetes, IFG, IGT, euglycemia, etc), therapeutic measures, and adherence,[26] thus limiting our ability to draw unequivocal conclusions.

In our cohort, we found that the overall compliance was affected mainly by the percentage of nights of CPAP usage (only 25% of subjects using it for more than 80% of the nights), whereas the median duration per night was slightly lower than the ones reported in other studies (median 4.8 h, 25% of patients using it for > 6.5 h). When analyzed with the prespecified criteria, we observed very low compliance rates, despite a "near-closed" healthcare system, very structured intake and follow-up, objective smart card and "cloud"-based readings of PAP usage, etc. Although this has been described before in veterans and associated with more prevalent daytime symptoms, higher comorbid load, posttraumatic stress disorder (which

may preclude mask acceptance),[38] disability claims, administrative issues, etc, these may not be the only explanations. The VAMONOS study included a significantly higher percentage of patients with mild OSA than other studies. As such, our cohort included mild, moderate, and severe OSA in 52%, 30%, and 18%, respectively. If 52% of patients had mild OSA (with an estimated range of 42% to 62% when inputting the cases with missing baseline AHI), poorer CPAP compliance rates may be less surprising, as prior literature showed that adherence to therapy is lower in mild sleep apnea. Additionally, very few studies followed patients on CPAP therapy for more than 6 mo. In a "real life," point-of-care patient population (i.e., not in the setting of randomized controlled trials), longer follow-up as in our study may be correlated with higher attrition rates. These findings may also be influenced by the fact that our sleep laboratory does not use respiratory effort related arousals for compilation of OSA severity metrics, which could have changed the percentage of patients with mild OSA.

Previous studies and a recent meta-analysis have shown that CPAP therapy may be associated with an increase in body weight and BMI, which may be intriguing in light of the correlations between insulin resistance and weight.[39] In our analyses, we were able to confirm these findings, as patients who met more stringent criteria for CPAP compliance had more weight gain than the ones lost to CPAP follow-up or those not meeting criteria (a dose-response effect?). One possible explanation may be that CPAP therapy could mitigate the catabolic effects induced by untreated sleep apnea (e.g., increases in catecholamines, cortisol, and sympathetic activity), thus creating—at least in the short term—an imbalance between catabolic and anabolic processes. In a study by Harsch et al.[40] on 40 patients with OSA, insulin sensitivity increased significantly after only 2 days of CPAP therapy; this short-term effect may be due to a reduced sympathetic activity,[23] confirming that OSA is an independent risk factor for insulin resistance. The effect of CPAP on insulin sensitivity, while it remained stable at 3 mo, was smaller in obese patients than in nonobese patients, suggesting perhaps that in obese individuals insulin sensitivity is linked mainly to adiposity and to a lesser extent to OSA.[40] Our cohort included only 7% normal-weighted individuals, whereas 64% were obese at baseline. Other explanations of how CPAP may lead to weight gain include: CPAP therapy leads to more daytime energy and less sleepiness, allowing perhaps more opportunities to eat, increase exercise and more muscle mass deposition, possible appetite enhancements, etc.

Our study has several strengths: its large size, lack of selection bias (as we included all consecutive patients), ethnic/racial diversity (i.e., better representation of African Americans than in other studies), acceptable period of follow-up (as many other trials span less than 6 mo), objective data for CPAP compliance from smart card and "cloud"-based system downloads, and a "near-closed" system that ensures better clinical and CPAP follow-up.

Our study also has several limitations. First, the patient population is from a single center and represented predominantly by males, sex distribution typical for veterans (only 15% to 20% women). Second, the duration of the study clinic follow-up is still relatively short (median 9, IQR 6–14 mo) in order to detect incident cardiovascular events, prediabetes, or diabetes; nevertheless, we were able to see some trends even during this period of follow-up, especially in more stringent categories of therapeutic adherence. Third, this was a nonrandomized, point-of-care, comparative effectiveness study, patients enrolled in this cohort being consecutive patients from three sleep clinics; although this may carry a referral bias (affecting its generalizability to other populations), it is an important addition to other randomized studies, which possess their own selection and generalizability biases. Fourth, as an observational study, there are several other inherent limitations: no control or sham CPAP group, no data on oral glucose tolerance testing, menopausal status or comorbid polycystic ovary syndrome, missing data points, etc. We also acknowledge that it is conceivable that other interventions, not captured here, such as dietary or exercise interventions, could have contributed. Longer term follow-up and confirmatory analyses are necessary.

CONCLUSIONS

In this comparative effectiveness study of a cohort of mostly obese and overweight patients seen in sleep clinics (VAMONOS study), we found that glucose metabolism parameters are influenced by superior adherence to CPAP therapy, even in the short term. Outstanding and excellent compliance had a superior effect on incident type 2 diabetes mellitus and impaired fasting glucose, despite higher gains in weight over the relatively short period of follow-up. Future interventional studies should control for lifestyle changes such as diet, exercise, nutritional support, etc, so that the glycemic effects attributable to positive airway pressure therapy could be assessed with higher precision and independent of ascertainment bias.

ABBREVIATIONS

AA, African-Americans
AHI, apnea-hypopnea index
BMI, body mass index
C, Caucasians
CPAP, continuous positive airway pressure
DM, diabetes mellitus
EDS, excessive daytime sleepiness
ESS, Epworth Sleepiness Scale
H_2O, water
HbA1c, hemoglobin A1c
HDL, high density lipoprotein
HOMA-IR, homeostatic model assessment of insulin resistance
IFG, impaired fasting glucose
IGT, impaired glucose tolerance
IQR, interquartile range
LDL, low density lipoprotein
Nl, normal
OSA, obstructive sleep apnea
PAP, positive airway pressure
PreDM, prediabetes mellitus

PSG, polysomnography
P95/P90, 95th or 90th percentile
REM, rapid eye movement
T2DM, type 2 diabetes mellitus
VA, Veterans Affairs
VAMONOS, Veterans Affairs' Metabolism, Obstructed and
  Non-Obstructed Sleep

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DISCLOSURE STATEMENT