Effect of Continuous Positive Airway Pressure on Glycemic Control in Patients with Obstructive Sleep Apnea and Type 2 Diabetes

A Randomized Clinical Trial

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Abstract

Rationale: Obstructive sleep apnea (OSA) is a risk factor for type 2 diabetes that adversely impacts glycemic control. However, there is little evidence about the effect of continuous positive airway pressure (CPAP) on glycemic control in patients with diabetes.

Objectives: To assess the effect of CPAP on glycated hemoglobin (HbA1c) levels in patients with suboptimally controlled type 2 diabetes and OSA, and to identify its determinants.

Methods: In a 6-month, open-label, parallel, and randomized clinical trial, 50 patients with OSA and type 2 diabetes and two HbA1c levels equal to or exceeding 6.5% were randomized to CPAP (n = 26) or no CPAP (control; n = 24), while their usual medication for diabetes remained unchanged.

Measurements and Main Results: HbA1c levels, Homeostasis Model Assessment and Qualitative Insulin Sensitivity Check Index scores, systemic biomarkers, and health-related quality of life were measured at 3 and 6 months. After 6 months, the CPAP group achieved a greater decrease in HbA1c levels compared with the control group. Insulin resistance and sensitivity measurements (in noninsulin users) and serum levels of IL-1β, IL-6, and adiponectin also improved in the CPAP group compared with the control group after 6 months. In patients treated with CPAP, mean nocturnal oxygen saturation and baseline IL-1β were independently related to the 6-month change in HbA1c levels ($r^2 = 0.510$, $P = 0.002$).

Conclusions: Among patients with suboptimally controlled type 2 diabetes and OSA, CPAP treatment for 6 months resulted in improved glycemic control and insulin resistance compared with results for a control group.

Clinical trial registered with www.clinicaltrials.gov (NCT01801150).

Keywords: sleep apnea; diabetes; insulin; glycemia; clinical trial

Obstructive sleep apnea (OSA) and type 2 diabetes are common comorbid conditions. Evidence has accumulated to indicate that OSA is associated with alterations in glucose metabolism, including insulin resistance and impaired glucose tolerance, independently of obesity (1–4). Moreover, OSA has been shown to be an independent risk factor for type 2 diabetes (5–10), and it has an adverse impact on glycemic control (11, 12) in patients with diabetes. To explain this association, it has been proposed that intermittent hypoxia and sleep fragmentation, caused by successive apnea–hypopnea episodes, may induce

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At a Glance Commentary

Scientific Knowledge on the Subject: Obstructive sleep apnea (OSA) has been identified as an independent risk factor for type 2 diabetes. However, the effect of continuous positive airway pressure (CPAP) on glycemic control in patients with diabetes and OSA as well as its potential mechanisms of action are not precisely understood.

What This Study Adds to the Field: This randomized controlled trial is specifically designed to study the effect of 24 weeks of CPAP on glycemic control in patients with suboptimally controlled type 2 diabetes and OSA. Our results indicate that CPAP prescription, compared with standard care, results in a statistically significant improvement of glycemic control and insulin resistance. Nocturnal hypoxemia and baseline IL-1β are identified as determinant factors for the 6-month improvement in glycemic control, and therefore a CPAP-induced reversion of the proinflammatory status seems to play an important role in HbA1c decrease.

several intermediate disorders, such as activation of the sympathetic nervous system, oxidative stress, systemic inflammation, alterations in appetite-regulating hormones, and activation of the hypothalamic–pituitary–adrenal axis. These, in turn, favor the development of insulin resistance, glucose intolerance, and poor glycemic control (13).

Continuous positive airway pressure (CPAP) therapy is an effective treatment for OSA. However, the effect of CPAP on the glycemic control of patients with diabetes is unclear (14). Some observational studies have reported that CPAP might improve insulin resistance (15, 16) or glycated hemoglobin (HbA1c) levels (17), but others failed to detect these effects (18, 19). In contrast, there is only a limited number of randomized controlled trials that evaluate the effect of CPAP on glycemic control in patients with diabetes, and their results are inconsistent. West and coworkers (20) and Comondore and coworkers (21) did not detect changes in HbA1c levels or insulin resistance after 3 and 1 months of CPAP treatment, respectively. Meanwhile, Weinstock and coworkers (22) reported an improvement in insulin sensitivity after 2 months of CPAP therapy. Nonetheless, it is possible that these studies were mainly limited by their short follow-up periods and inclusion of patients with various degrees of glycemic control.

The objective of our study was to conduct a randomized controlled trial to assess the 6-month effect of CPAP treatment on the glycemic control and insulin resistance of patients with suboptimally controlled type 2 diabetes and OSA. We also aimed to identify independent determining factors for the potential decrease in HbA1c levels induced by CPAP therapy.

Methods

Study Design and Patients

An open-label, randomized, clinical trial of parallel groups was conducted in patients diagnosed with type 2 diabetes and OSA (clinicaltrials.gov identifier, NCT01801150).

Subjects aged 18–80 years, with a body mass index between 25 and 39.9 kg/m^2, a previous diagnosis of type 2 diabetes without changes in diabetes medication in the previous month, two successive HbA1c values greater than 6.5% (minimum interval of 2 mo), and who agreed not to change diabetes medication during the trial unless medically indicated were eligible for study enrollment. Exclusion criteria included respiratory failure, morbid obesity, disabling hypersomnia requiring urgent treatment (Epworth Sleepiness Scale [ESS] score, $\geq$18), or current use of CPAP treatment. The study protocol was approved by the Ethics Committee of the Hospital Universitario La Paz (HULP PI-907) and participants provided written informed consent.

Procedures

Potential participants were screened for OSA with a conventional respiratory polygraph (Alice PDx; Respironics, The Netherlands), and polygraphy data were analyzed by trained personnel, using standard criteria (23). Information regarding diabetes characteristics, medication use, sleepiness (ESS score), 24-hour blood pressure, comorbidity, and biochemical assessment were recorded for each patient at inclusion. The Charlson Comorbidity Index was calculated and dyslipidemia and hypertension were recorded.

Intervention

Patients with an apnea–hypopnea index (AHI) equal to or exceeding 5 were randomly assigned at a 1:1 ratio to receive either CPAP treatment or no active intervention. For those patients randomized to CPAP treatment, optimal pressure was titrated with an auto-CPAP device (AutoSet; ResMed, Sydney, Australia) (24). All participants received sleep hygiene advice and dietary counseling, although there was no specific weight loss program.

The CPAP device used (S9; ResMed) recorded all the data from the 6 months of use. Adherence was considered adequate if CPAP use was at least 4 hours every night.

Study Endpoints

The primary study outcome was change in HbA1c levels from baseline to 6 months. Secondary outcomes included change in 3- and 6-month fasting glucose and insulin levels, Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) and Qualitative Insulin Sensitivity Check Index (QUICKI) scores, biomarker levels, and health-related quality of life.

Patients were evaluated at baseline and 3 and 6 months afterward. At each visit, physicians recorded anthropometric characteristics, medications, alcohol and tobacco consumption, ESS score, adherence to CPAP and antidiabetic treatment, daily physical activity, and health-related quality of life. Fasting glucose, insulin, and HbA1c levels were measured, and in noninsulin users HOMA-IR (25) and QUICK (26) scores were calculated. Serum levels of IL-1β, IL-6, IL-8, tumor necrosis factor-α, leptin, adiponectin, neuropeptide Y, and 8-isoprostane were determined by immunoassay; plasma lipid levels, thyroid-stimulating hormone, growth factor, and insulin-like growth factor-1 were also determined.

Daily physical activity was assessed using the London Chest Activity of Daily Living (LCADL) scale, whereas health-related quality of life was assessed with the Short-Form Health Survey (SF-12) and the Diabetes Quality of Life (DQoL) questionnaires.

Additional details on methods are provided in the online supplement.

Statistical Analysis

Data are summarized as means ± SD, medians (interquartile range), or frequencies. Between-group baseline comparisons were based on two-sample *t*, Mann–Whitney, or χ^2 tests. The intragroup differences from the beginning to the end of the study were evaluated with a paired *t* test.

Primary outcome analysis used the intention-to-treat principle and included all participants as randomized. Missing values for the main outcome measurements were replaced by multiple imputation with multivariate normal regression. Intergroup comparisons of the change in HbA1c (follow-up to baseline) and other outcomes were assessed by analysis of covariance to adjust for baseline values. Sex, age, AHI, minimum nocturnal oxygen saturation, ESS score, dyslipidemia and Charlson Comorbidity Index score were also included as covariates. A per-protocol analysis based on data from patients with adequate adherence to CPAP was also performed.

Variables related to HbA1c reduction were determined by Pearson correlation and simple regression analysis using weighted least squares. Those significant contributors were then input into a stepwise multiple linear regression analysis to identify independent determinants of the change in HbA1c levels. A two-sided *P* value less than 0.05 was considered significant.

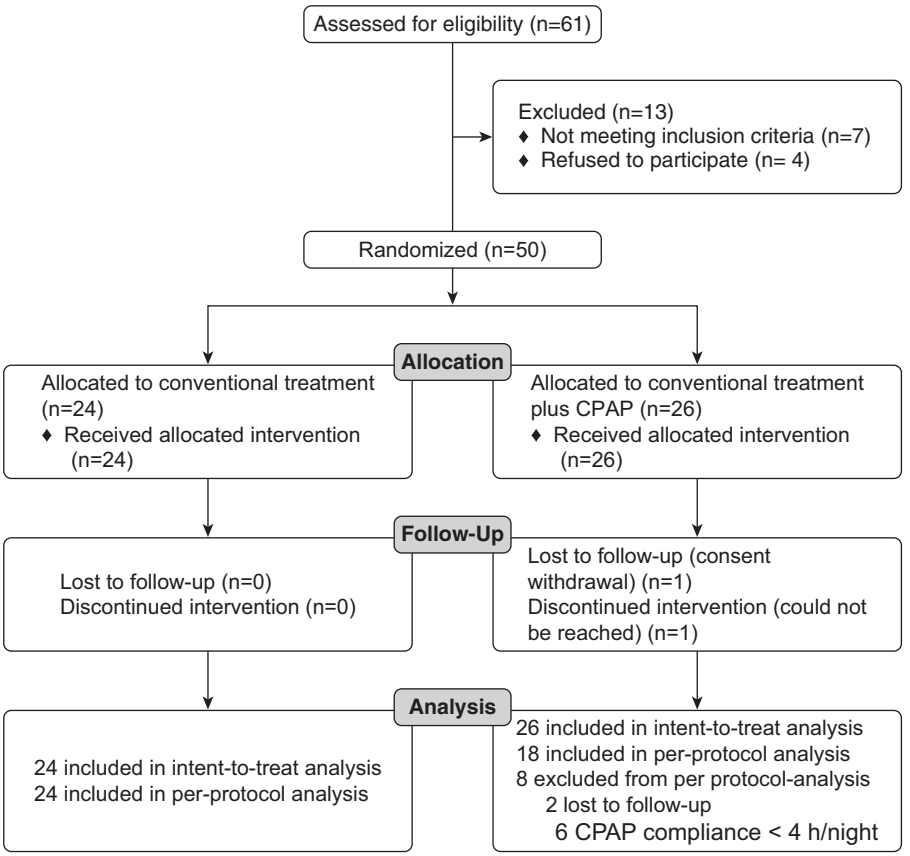

Figure 1. Patient flow diagram. CPAP = continuous positive airway pressure.

Results

The flow of study participants is shown in Figure 1. Of 61 screened patients, 50 met the inclusion criteria and were randomized: 26 to the CPAP group and 24 to the control group. Two participants randomized to the CPAP group were lost to follow-up: one participant due to consent withdrawal and another due to change of residence. Patients who did not complete the follow-up were similar to those who did in terms of demographics and/or characteristics contributing to outcomes between study groups.

Baseline characteristics were similar between the CPAP and control groups (Table 1). At enrollment, participants had a mean HbA1c level of 7.62 ± 1.05% and a mean AHI of 32.1 ± 20.9 events per hour. No patient had central sleep apnea.

Out of the 50 randomized participants, 29 (58%) used oral hypoglycemic agents alone, 3 (6%) used insulin alone, and 18 (36%) used both. The use of antidiabetic medications is detailed in Table E1 in the online supplement.

The average use of CPAP treatment was 5.2 ± 1.9 hours per night, with 20 patients (76.9%) using it at least 4 hours per night. The mean CPAP used was 8.1 ± 1.3 cm H_2O.

Changes in anthropometric characteristics, body composition and daily physical activity are shown Table E2. All of these measurements remained stable during follow-up, with no significant differences between groups. There was no significant measurable change in use of antidiabetic, antihypertensive, or lipid-lowering medications, nor was there a between-group difference in medication use.

Table 2 and Figure 2 summarize results for baseline, follow-up, and change in HbA1c levels between the groups. In the intention-to-treat analysis of this primary outcome, the adjusted 6-month CPAP effect on HbA1c levels was −0.4% (95% confidence interval [CI], −0.7% to −0.04%; *P* = 0.029). Imputed values for HbA1c levels were calculated on the basis of a linear regression model for the two patients with missing follow-up measurements due to failure to complete the protocol. Sensitivity analyses using baseline observations carried forward for missing values and with data only from patients who completed the study produced similar outcomes. These HbA1c changes were also significant with no imputation (Table E3). In contrast, analyses did not reveal between-group differences in HbA1c values after 3 months.

The per-protocol analysis (18 patients in the CPAP group and 24 patients in the control group) produced similar results. Compared with the control group, the participants in the CPAP group showed a statistically significant decrease in HbA1c levels after 6 months (adjusted treatment effect, –0.5% [95% CI, −0.9 to −0.09%]; *P* = 0.017), whereas there were no significant differences between groups after 3 months (Table E4).

Changes in fasting glucose and insulin levels as well as insulin resistance and sensitivity indices are also summarized in Table 2. Compared with the control group,

Table 1. Baseline Characteristics of All Randomized Patients*

	All Patients	Control Group	CPAP Group	*P* Value
No. of participants	50	24	26	
Women, n (%)	20 (40)	12 (69)	8 (31)	0.136
Age, yr	61 ± 9	62 ± 10	60 ± 9	0.426
Body mass index, kg/m^2	32.5 ± 4.5	32.4 ± 4.4	32.6 ± 4.6	0.855
Fat mass index, kg/m^2	12.7 ± 3.9	13.2 ± 4.0	12.2 ± 3.8	0.358
Neck circumference, cm	41.9 ± 4.1	41.1 ± 3.8	42.7 ± 4.3	0.153
Waist-to-hip ratio	0.99 ± 0.07	0.99 ± 0.07	1.00 ± 0.07	0.719
Smoking history, n (%)				0.506
Current	12 (24)	4 (17)	8 (31)	
Former	19 (38)	10 (42)	9 (35)	
Never	19 (38)	10 (42)	9 (35)	
Years since diabetes diagnosis	5 (3–15)	7 (3.5–24.5)	4.5 (2.25–10.75)	0.091
Patients with baseline hemoglobin A1c, n (%)				0.673
⩾6.5 to <7.0%	13 (26)	6 (25)	7 (27)	
⩾7.0 to <8.0%	23 (46)	10 (42)	13 (50)	
⩾8.0 to 9.0%	11 (22)	7 (29)	4 (15)	
⩾9.0%	3 (6)	1 (4)	2 (8)	
Hypoglycemic medications, n (%)				0.775
Oral agents only	29 (58)	13 (54)	16 (62)	
Insulin only	3 (6)	1 (4)	2 (8)	
Combination drugs	18 (36)	10 (42)	8 (31)	
Sleep characteristics				
Epworth Sleepiness Scale score	7.7 ± 4.3	8.0 ± 3.7	7.4 ± 4.8	0.570
Apnea–hypopnea index, h^{-1}	32.1 ± 20.9	28.2 ± 17.4	35.6 ± 23.4	0.204
Desaturation index, h^{-1}	30.7 ± 22.8	26.2 ± 18.9	35.4 ± 25.9	0.184
$TSat_{90}$, %	10.4 (2.3–46.6)	8.8 (1.6–33.4)	10.4 (4.4–51.9)	0.344
Mean nocturnal oxygen saturation, %	91.5 ± 2.3	91.8 ± 2.1	91.1 ± 2.5	0.286
Minimum nocturnal oxygen saturation, %	76.4 ± 9.1	76.5 ± 9.3	76.2 ± 9.1	0.909
Comorbidity				
Charlson Comorbidity Index	3 (2–4)	3 (2–4)	3 (2–4)	0.834
Hypertension, n (%)	39 (78)	21 (88)	18 (69)	0.111
Dyslipidemia, n (%)	36 (72)	20 (83)	16 (62)	0.080
Coronary heart disease, n (%)	4 (3)	1 (4)	3 (12)	0.336
Systolic blood pressure, mm Hg	127 ± 14	126 ± 13	128 ± 15	0.684
Diastolic blood pressure, mm Hg	74 ± 9	73 ± 8	76 ± 11	0.308
Total cholesterol, mg/dl	178 ± 42	179 ± 46	177 ± 39	0.865
HDL cholesterol, mg/dl	45 ± 11	46 ± 11	45 ± 11	0.710
LDL cholesterol, mg/dl	109 ± 35	112 ± 33	107 ± 37	0.602
Triglycerides, mg/dl	168 ± 74	164 ± 54	172 ± 89	0.715

Definition of abbreviations: CPAP = continuous positive airway pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; $TSat_{90}$ = night time spent with oxygen saturation below 90%.
SI conversion factors: To convert glucose values to mmol/L, multiply by 0.0555; total cholesterol, LDL-cholesterol, and HDL-cholesterol values to mmol/L, multiply by 0.0259; and insulin to pmol/L, multiply by 6.945.
*Values represent mean ± SD, median (interquartile range), or n (%).

insulin sensitivity assessed by QUICKI improved significantly after 3 months of CPAP treatment (adjusted between-group difference, 0.034 [0.002–0.066]; $P = 0.038$) and was sustained up to 6 months (adjusted between-group difference, 0.055 [0.013–0.096]; $P = 0.013$). After 6 months, the HOMA-IR also improved in the treatment group compared with the control group (adjusted between-group difference, −2.58 [95% CI, −4.75 to −0.41]; $P = 0.023$) (Figure 2). Similar results were obtained in the preprotocol analysis (Table E4).

Baseline and follow-up values of systemic biomarkers, other biochemical parameters, and health-related quality of life across the groups are summarized in Table 3 and in Tables E5 and E6. As for the control group, patients treated with CPAP for 6 months showed lower levels of IL-1β and IL-6 as well as higher levels of adiponectin (Table 3). After 6 months, a significant reduction in the concentration of low-density lipoprotein cholesterol was also found in the CPAP group compared with the control group ($P = 0.042$). Indeed, patients treated with CPAP for 6 months experienced an improvement in satisfaction with the treatment domain of the DQoL questionnaire compared with control participants ($P = 0.043$), with no other significant changes in the other domains or total score.

The relationship between the absolute change in HbA1c after 6 months of CPAP therapy and the baseline characteristics of the subjects are shown in Table E7. A significant correlation was found for baseline HbA1c, sleep apnea severity assessed by AHI, desaturation index, mean nocturnal oxygen saturation, and baseline IL-1β level (Figure 3).

In contrast, no correlation was found between the other biomarkers or the number of hours of CPAP use and the decrease in HbA1c levels. From among the related factors, in a stepwise multiple

Table 2. Effect of Continuous Positive Airway Pressure Treatment on Glucose Metabolic Parameters in the Intention-to-Treat Population*

	CPAP Group		Control Group		Intergroup Crude Difference		Intergroup Adjusted Difference	
	Baseline	Follow-up	Baseline	Follow-up	Difference (95% CI)†	*P* Value	Difference (95% CI)‡	*P* Value
Hemoglobin A1c, %								
After 3 mo	7.6 ± 1.3	7.7 ± 1.2	7.6 ± 0.7	7.5 ± 1.6	0.006 (−0.6 to 0.6)	0.983	0.1 (−0.6 to 0.7)	0.873
After 6 mo		7.3 ± 1.1		7.6 ± 0.7	−0.4 (−0.7 to −0.1)	0.024	−0.4 (−0.7 to −0.04)	0.029
Fasting glucose, mg/dl								
After 3 mo	168 ± 38	162 ± 43	169 ± 40	166 ± 72	−3 (−37 to 31)	0.860	1 (−37 to 38)	0.978
After 6 mo		159 ± 38		162 ± 61	−4 (−34 to 26)	0.780	−23 (−53 to 6)	0.117
Fasting plasma insulin,§ μU/ml								
After 3 mo	17.4 ± 5.7	15.3 ± 6.0	16.7 ± 4.1	18.1 ± 6.2	−3.2 (−7.7 to 1.2)	0.150	−4.0 (−10.3 to 2.3)	0.194
After 6 mo		13.4 ± 7.1		18.8 ± 5.2	−5.7 (−10.6 to 0.9)	0.022	−5.7 (−11.5 to 0.2)	0.056
HOMA-IR†								
After 3 mo	6.73 ± 2.08	5.89 ± 2.33	6.90 ± 1.25	7.07 ± 1.72	−1.19 (−2.65 to 0.27)	0.107	−1.56 (−3.40 to 0.28)	0.092
After 6 mo		5.12 ± 2.77		6.94 ± 1.59	−1.81 (−3.47 to −0.15)	0.033	−2.58 (−4.75 to −0.41)	0.023
QUICKI†								
After 3 mo	0.494 ± 0.074	0.502 ± 0.039	0.478 ± 0.019	0.473 ± 0.027	0.024 (−0.0002 to 0.048)	0.052	0.034 (0.002 to 0.066)	0.038
After 6 mo		0.525 ± 0.059		0.469 ± 0.024	0.052 (0.017 to 0.087)	0.005	0.055 (0.013 to 0.096)	0.013

Definition of abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure; HOMA-IR = Homeostasis Model Assessment–Insulin Resistance; QUICKI = Quantitative Insulin Sensitivity Check Index.
Values represent means ± SD.
*Intergroup differences were calculated as (change in CPAP group) − (change in control group).
†Adjusted for baseline values.
‡Adjusted for baseline values, center, sex, age, body mass index, apnea–hypopnea index, minimum nocturnal oxygen saturation, Epworth Sleepiness Score, dyslipidemia, and Charlson index.
§Limited to noninsulin users: n = 16 in treatment group, n = 13 in control group.

regression model only mean nocturnal oxygen saturation and IL-1β level were retained as independent variables ($r^2 = 0.510$, $P = 0.002$) (Table 4).

Interestingly, a direct relationship was found between the change in IL-1β levels after 6 months and the change in HbA1c levels for both the study subjects overall ($r = 0.457$, $P = 0.001$) and only for patients treated with CPAP ($r = 0.449$, $P = 0.028$) (Figure 4).

Discussion

To our knowledge, this randomized controlled trial is the first designed specifically to examine the effect of 24 weeks of CPAP on glycemic control in patients with suboptimally controlled type 2 diabetes and OSA. Our results indicate that CPAP prescription, compared with standard care, results in a statistically significant improvement of glycemic control and/or insulin resistance. Moreover, baseline nocturnal hypoxemia and IL-1β levels were identified as determining factors for the CPAP-induced improvement in glycemic control.

A methodological aspect that merits comment is the choice of the cut-point used in our study to define suboptimal glycemic control. In contrast with the general target of HbA1c less than 7.0%, some major randomized clinical trials provide evidence indicating that an intensive glycemic control strategy (goal HbA1c, <6.5%) could diminish the development of micro- and macrovascular complications in patients with diabetes with cardiovascular risk (27–29). In fact, it has been demonstrated that patients with type 2 diabetes and mild-to-moderate cardiovascular risk, as is the case of many patients with OSA, develop fewer cardiovascular events when an intensive glycemic control strategy is established, based on HbA1c levels less than 6.5% (30).

The data available about the effect of CPAP on glucose metabolism in patients with type 2 diabetes are limited and present different levels of quality. Apart from observational studies, previous clinical trials have not detected a CPAP effect. In a randomized, parallel, controlled study, West and coworkers (20) allocated 42 men with type 2 diabetes to receive therapeutic or sham CPAP for 3 months, and they found no differences in glycemic control or insulin resistance (assessed by the HbA1c and HOMA score, respectively). However, the diagnosis of OSA was done with an unconventional criterion, and CPAP compliance was low. In an even smaller sample of 13 subjects with type 2 diabetes and OSA with minimal daytime sleepiness, Comondore and coworkers (21) were also not able to identify any effect on HbA1c or HOMA score after 1 month of treatment. In addition to the short treatment duration, the lack of effect in this case was probably related to the good glycemic control of their patients (baseline HbA1c, 5.8%), so the margin for potential improvement was limited.

Our results partially agree with these studies, as CPAP did not significantly change HbA1c levels after 3 months in the treatment group versus the control group. However, when CPAP treatment was maintained for 6 months, there was a significant reduction in HbA1c levels, showing the need for a prolonged treatment time. In fact, it has been speculated that structural changes due to pancreatic beta-cell damage in patients with diabetes may require longer intervention times to be corrected (14). Likewise, other authors have suggested that, to achieve a clinically significant improvement in the glycemic control of patients with type 2 diabetes, it might be

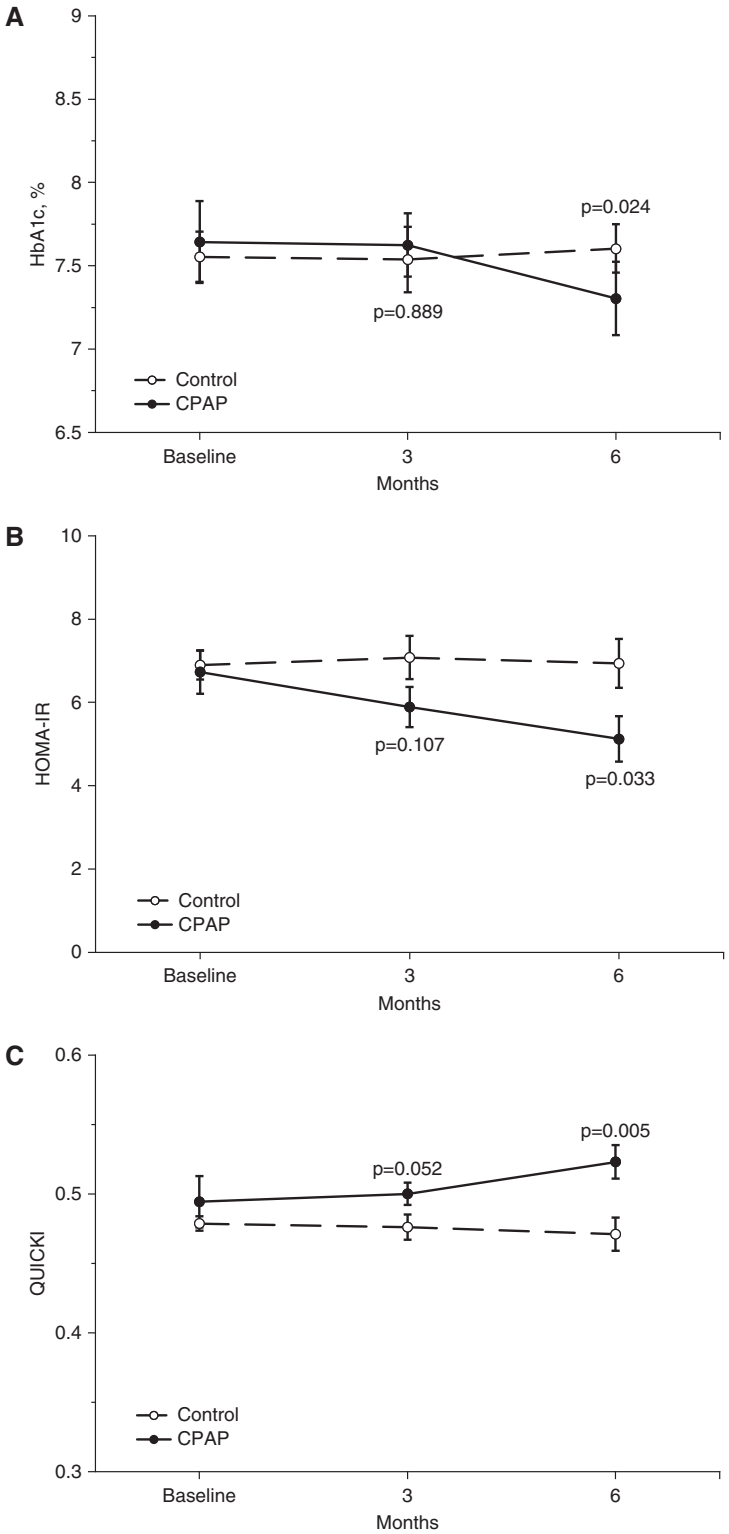

Figure 2. Evolution of (*A*) glycated hemoglobin levels and (*B*) insulin resistance and (*C*) insulin sensitivity indices. Unadjusted mean values are presented for groups in the intention-to-treat analysis. *Error bars* represent SEs. Insulin sensitivity variables represent data only from patients not using insulin (n = 29). Intergroup comparisons were assessed by analysis of covariance to adjust for baseline values. CPAP = continuous positive airway pressure; HbA1C = glycated hemoglobin; HOMA-IR = Homeostasis Model Assessment–Insulin Resistance; QUICKI = Quantitative Insulin Sensitivity Check Index.

necessary to extend CPAP use for more time per night (31).

Nonetheless, it is possible that insulin sensitivity responds earlier to the CPAP effect, which is suggested by the improvement in the QUICKI score of our patients after 3 months of CPAP treatment. This finding agrees with another previous clinical trial that, in nondiabetic patients with impaired glucose tolerance and severe OSA, detected an improvement in the insulin sensitivity index (another indirect measurement of insulin sensitivity derived from the 2-h oral glucose tolerance test) after 2 months of CPAP treatment (22).

To contemplate the potential clinical relevance of the CPAP effect detected in our study, we must keep in mind that an absolute decrease of 1% in HbA1c levels has been associated with a 15–21% decrease in major cardiovascular disease events and a 37% decrease in microvascular complications of patients with diabetes (32–34). Thus, our observed reduction of 0.4% in HbA1c levels might be expected to produce a 6–8% decrease in cardiovascular disease risk and a 15% reduction in risk of microvascular complications. This effect could be even greater if we consider that in these patients CPAP also caused a decrease in low-density lipoprotein cholesterol, which reduces the risk of macrovascular events in patient populations with diabetes (35). Furthermore, it is important to highlight that in this present study we have randomized patients with OSA with an AHI of 5 or greater. Therefore, it seems that the action of CPAP on glycemic control is not limited to patients with severe OSA, but there could also be a margin for early intervention in patients with mild or moderate OSA.

The improved glycemic control of our patients does not seem attributable to treatment modifications, weight loss, or increased daily physical activity, because these parameters remained unchanged during the follow-up period. Although the mechanisms responsible for CPAP-induced improvement in glycemic control and insulin resistance in this study cannot be determined with certainty, it seems probable that they are related to the reversion of some mechanism by which OSA alters glucose metabolism. In our case, it is possible that hypoxia and inflammatory stress might have a particularly important role because mean nocturnal oxygen saturation and IL-1β level were retained as independent factors

Table 3. Effect of Continuous Positive Airway Pressure Treatment on Systemic Biomarkers in the Intention-to-Treat Population*

	CPAP Group		Control Group		Intergroup Crude Difference		Intergroup Adjusted Difference	
	Baseline	Follow-up	Baseline	Follow-up	Difference (95% CI)†	*P* Value	Difference (95% CI)‡	*P* Value
Leptin, ng/ml								
After 3 mo	2.5 ± 1.8	1.9 ± 1.0	2.4 ± 1.9	2.1 ± 1.1	−0.2 (−0.8 to 0.4)	0.511	−0.07 (−0.4 to 0.2)	0.656
After 6 mo		1.9 ± 0.6		2.1 ± 0.5	−0.2 (−0.5 to 0.1)	0.228	−0.1 (−0.5 to 0.2)	0.375
Adiponectin, ng/ml								
After 3 mo	370 ± 204	417 ± 273	346 ± 152	367 ± 300	33 (−112 to 178)	0.647	66 (−96 to 227)	0.414
After 6 mo		470 ± 130		366 ± 113	102 (32 to 172)	0.005	91 (27 to 156)	0.007
IL-6, pg/ml								
After 3 mo	11.1 ± 4.7	9.1 ± 4.1	11.6 ± 4.4	11.4 ± 4.5	−2.2 (−4.6 to 0.2)	0.074	−2.2 (−4.7 to 0.3)	0.080
After 6 mo		8.0 ± 4.6		10.4 ± 3.5	−2.2 (−4.4 to −0.02)	0.048	−2.5 (−4.8 to −0.2)	0.036
IL-8, pg/ml								
After 3 mo	10.7 ± 3.3	10.5 ± 6.0	10.6 ± 2.9	11.2 ± 7.3	−0.7 (−4.2 to 2.8)	0.705	0.5 (−3.1 to 4.0)	0.793
After 6 mo		9.7 ± 4.0		9.6 ± 3.7	0.1 (−2.1 to 2.3)	0.946	1.0 (−1.5 to 3.5)	0.425
TNF-α, pg/ml								
After 3 mo	5.4 ± 2.6	6.0 ± 1.3	5.2 ± 2.2	6.0 ± 2.0	−0.1 (−1.1 to 0.8)	0.768	−0.2 (−1.3 to 0.9)	0.735
After 6 mo		5.4 ± 2.1		5.5 ± 2.6	−0.2 (−1.5 to 1.1)	0.773	0.07 (−1.2 to 1.4)	0.909
IL-1β, pg/ml								
After 3 mo	2.49 ± 1.29	1.85 ± 0.57	2.12 ± 0.90	2.17 ± 0.91	−0.3 (−0.8 to 0.1)	0.160	−0.4 (−0.9 to 0.1)	0.125
After 6 mo		1.08 ± 0.89		1.98 ± 1.04	−0.9 (−1.5 to −0.4)	0.001	−0.8 (−1.4 to −0.1)	0.018
8-Isoprostane, pg/ml								
After 3 mo	8.7 ± 3.2	8.5 ± 3.0	9.7 ± 4.3	9.2 ± 4.5	−0.6 (−2.8 to 1.6)	0.560	−0.6 (−3.2 to 1.9)	0.616
After 6 mo		7.0 ± 4.2		6.3 ± 4.3	0.4 (−2.0 to 2.9)	0.713	−0.6 (−2.5 to 1.3)	0.509
Neuropeptide Y, pg/ml								
After 3 mo	9.9 ± 4.0	9.0 ± 3.2	10.3 ± 4.5	8.9 ± 4.7	1.5 (−1.6 to 4.6)	0.315	−0.9 (−7.0 to 5.2)	0.672
After 6 mo		9.9 ± 4.3		9.1 ± 5.7	1.2 (−2.6 to 6.0)	0.308	0.1 (−6.4 to 6.6)	0.586

Definition of abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure; TNF-α = tumor necrosis factor-α.
Values represent means ± SD.
*Intergroup differences were calculated as (change in CPAP group) − (change in control group).
†Adjusted for baseline values.
‡Adjusted for baseline values, center, sex, age, body mass index, apnea–hypopnea index, minimum nocturnal oxygen saturation, Epworth Sleepiness score, dyslipidemia, and Charlson index.

related to the CPAP-induced HbA1c decrease.

In patients with OSA treated with CPAP, the elimination of intermittent hypoxia might improve the regulation of carbohydrate metabolism because hypoxia is accepted as one of the main determinants of HbA1c in these patients (13, 36). In fact, in patients with OSA and type 2 diabetes, it has been reported that HbA1c levels are more dependent on oxygen saturation than on AHI (36). The effect of hypoxia on glycemic control might be mediated by hypoxia-inducible factor-1, which triggers the expression of specific genes in the presence of low oxygen levels (37). So, in diabetic rats, an increase in hypoxia-inducible factor-1 expression by pancreatic beta cells, which inhibits glucose transport and perpetuates a state of insulin resistance, has been reported (38).

Although our results do not exclude the potential contribution of appetite-regulating hormones, oxidative stress, or the sympathetic nervous system to the CPAP effect on glycemic control, the identification of baseline IL-1β levels as an independent determining factor for HbA1c decrease, and especially the direct relationship found between HbA1c and IL-1β changes, highlight a potentially relevant role for inflammatory status. In fact, several reports confirm that proinflammatory cytokines contribute to functional disorders of the pancreatic islet cells and participate in the pathogenesis and progression of diabetes (39, 40). IL-1β is one of the most important proinflammatory cytokines, and experimental data have shown that human beta cells are susceptible to both IL-1β destruction and functional impairment, indicating a possible role in the pathogenesis and progression of type 2 diabetes (39–42).

Moreover, several clinical trials have reported that IL-1β–blocking therapies produce a reduction in HbA1c in patients with type 2 diabetes, potentially by an improvement of beta-cell function secondary to a decrease in the inflammatory process (43–45).

In our case, it seems possible that hypoxia may have a particularly important role given that mean nocturnal oxygen saturation was the only independent factor related to the decrease in HbA1c levels.

The major strength of our study is its randomized clinical trial design, long follow-up period, and selection of patients with suboptimal control of their diabetes, in whom there is a greater margin for improvement. Furthermore, all the patients included in the present study were

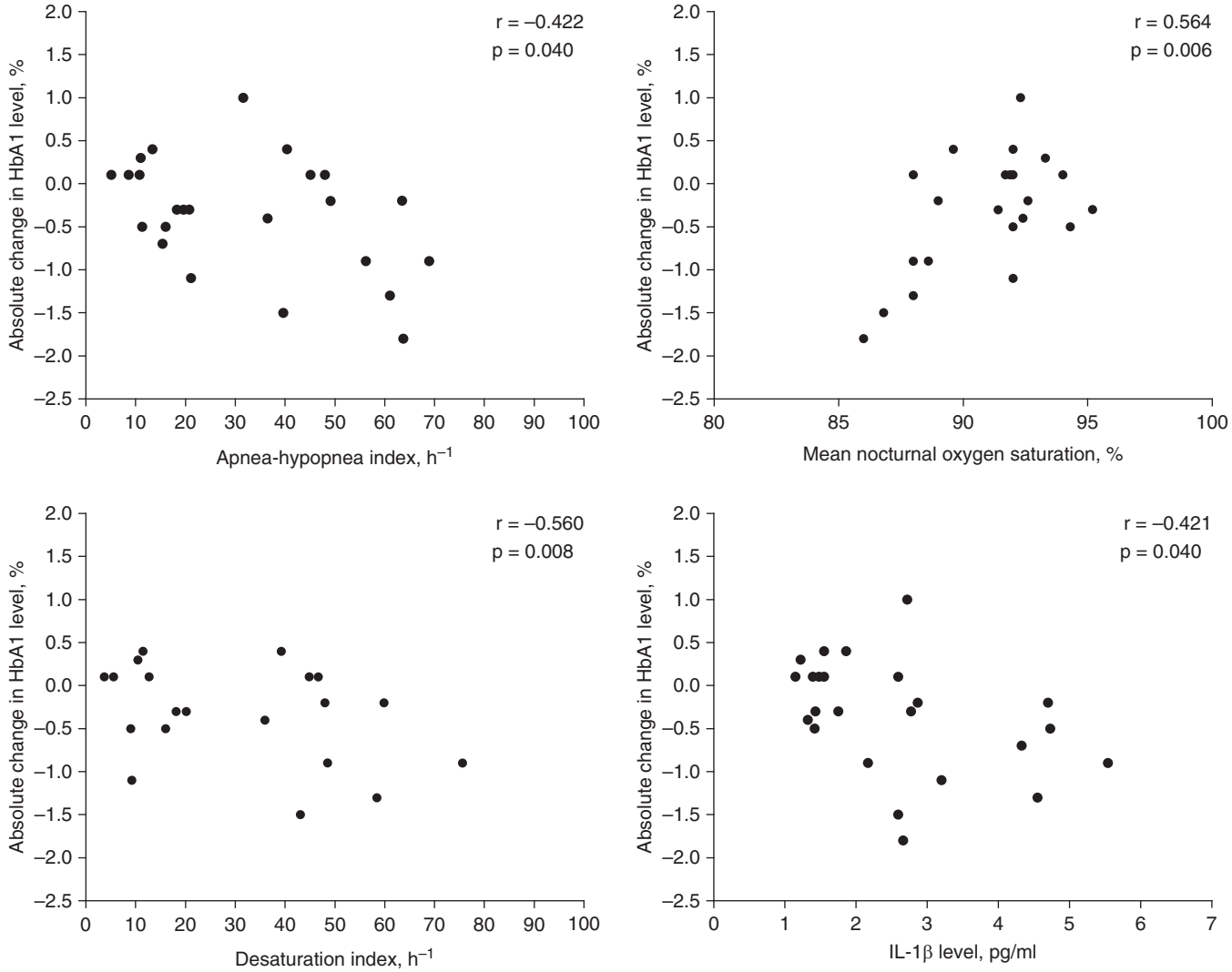

Figure 3. Correlation between changes in glycated hemoglobin (HbA1c) levels after 6 months of continuous positive airway pressure (CPAP) therapy (6 months – baseline) and sleep parameters and baseline IL-1β level. The analysis was performed in CPAP group patients who completed follow-up (n = 24).

referred from diabetes units or their primary care physicians; thus they are representative of standard clinical practice. This fact provides for the generalization of our results.

Nevertheless, this trial also has several limitations: (*1*) It is a study with a small sample size, although sufficient to detect response to treatment; (*2*) we chose not to use sham CPAP as a placebo because it is difficult to maintain its mid-term use without the patient realizing that he/she is not receiving effective treatment (46, 47). In fact, lower compliance with sham CPAP has been reported compared with optimal

Table 4. Independent Determinants of Decrease in Hemoglobin A1c Levels after 6 Months of Continuous Positive Airway Therapy

	Unstandardized Regression Coefficients		95% CI for *B*		Standardized Regression Coefficient: *B*	*P* Value	r^2	r^2 Change
	B	SE	Lower Limit	Upper Limit				
Constant	10.828	4.062	2.258	19.398	—	0.016	—	—
Mean nocturnal oxygen saturation, %	−0.120	0.044	−0.213	−0.027	−0.482	0.014	0.353	0.353
IL-1β, pg/ml	0.210	0.090	0.020	0.400	0.412	0.032	0.510	0.157

Definition of abbreviation: CI = confidence interval.

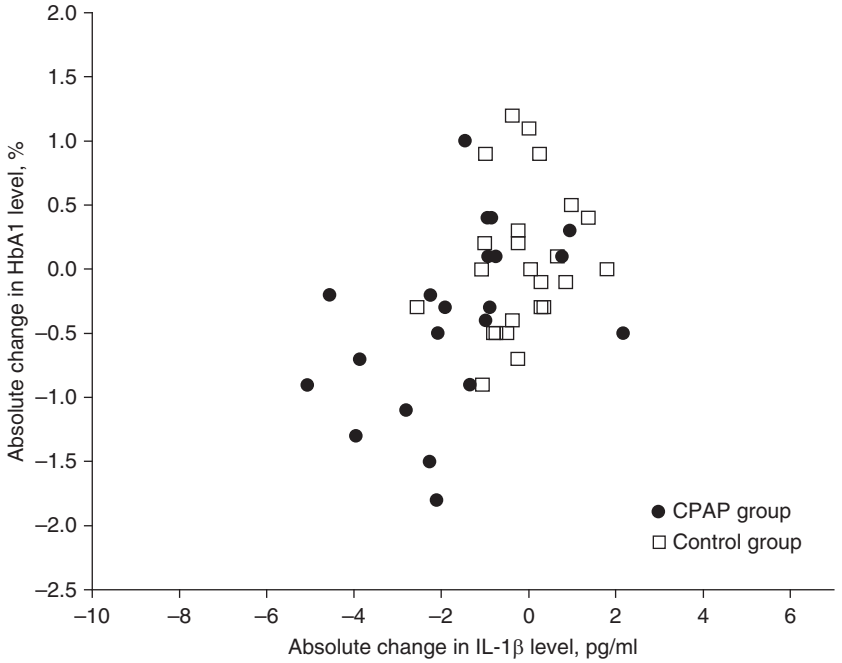

Figure 4. Relationship between change in IL-1β levels and change in glycated hemoglobin (HbA1c) levels in the continuous positive airway pressure (CPAP) group (*solid circles*) and control group (*open squares*); correlations were significant both for patients with obstructive sleep apnea treated with CPAP ($r = 0.449$, $P = 0.028$) and overall patients ($r = 0.457$, $P = 0.001$).

CPAP, suggesting that this device fails to function as a true placebo (48, 49); (*3*) the trial was not blind, although the main study variables were assessed objectively by technicians not involved in the study and blinded to patient allocation; (*4*) the selection of patients with an AHI equal to or exceeding 5 events/hour can minimize the effect of CPAP detected, as patients with mild OSA may have lower CPAP compliance than patients with moderate-to-severe OSA; (*5*) although not significant, the imbalance in the sex distribution between the two study groups, due to the lack of sex-stratified randomization, cannot rule out the existence of a sex-dependent factor in the metabolic response to CPAP; (*6*) small changes in medication (below the thresholds defined for insulin and oral hypoglycemic agents) cannot be excluded as playing a role in the CPAP effect on HbA1c; and (*7*) we used fixed CPAP because it is the less expensive, more widely used treatment, and therefore our data cannot be extrapolated to other treatment modalities such as auto-CPAP devices.

In conclusion, among patients with suboptimally controlled type 2 diabetes and OSA, CPAP treatment for 24 weeks resulted in improved glycemic control and insulin resistance when compared with the results for the control group. In these patients, CPAP-induced reversion of proinflammatory status seems to play an important role in HbA1c reduction. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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