Published in final edited form as:

Sleep Med. 2016 June ; 22: 57–60. doi:10.1016/j.sleep.2016.06.005.

Does enhanced insulin sensitivity improve sleep measures in patients with obstructive sleep apnea: A randomized, placebo-controlled pilot study

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Abstract

Background—High fasting insulin levels have been reported to predict development of observed apneas, suggesting that insulin resistance may contribute to the pathogenesis of obstructive sleep apnea (OSA). The study aim was to determine whether enhancing insulin sensitivity in individuals with OSA would improve sleep measures.

Patients/Methods—Insulin-resistant, nondiabetic individuals with untreated OSA were randomized (2:1) to pioglitazone (45mg/day) or placebo for 8 weeks in this single-blind study. All individuals had repeat measurements pertaining to sleep (overnight polysomnography and Functional Outcomes of Sleep Questionnaire) and insulin action (insulin suppression test).

Results—Forty-five overweight/obese men and women with moderate/severe OSA were randomized to pioglitazone (n=30) or placebo (n=15). Although insulin sensitivity increased 31% among pioglitazone-treated as compared to no change among individuals receiving placebo (($p < 0.001$ for between-group difference), no improvements in quantitative or qualitative sleep measurements were observed.

Conclusions—Pioglitazone administration increased insulin sensitivity in otherwise untreated individuals with OSA, without any change in polysomnographic sleep measures over an 8-week period. These findings do not support a causal role for insulin resistance in the pathogenesis of OSA.

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Clinical trial number: NCT02192684, ClinicalTrials.gov

Conflict of interest: The authors report there are no relevant conflicts of interest.

Keywords

Obstructive sleep apnea; pioglitazone; insulin resistance; prediabetes

Introduction

There is evidence [1] that fasting hyperinsulinemia, a surrogate estimate of insulin resistance [2], predicts development of obstructive sleep apnea (OSA). Furthermore, this relationship remained after accounting for adiposity [1], an important confounder since obesity is an established risk factor for OSA [3]. The possibility that insulin resistance might contribute to the genesis of OSA has also been raised by studies showing an increased prevalence of OSA in women with the polycystic ovary syndrome (PCOS) [4, 5], an insulin resistant state [6], and evidence that women with PCOS and OSA are more insulin-resistant than those with PCOS alone [7]. However, the results of the population-based study suggesting that insulin resistance predicted incident OSA were based upon use of a surrogate estimate of insulin resistance, and the presence of disordered sleep assessed by questionnaire, not polysomnographic (PSG) measurements [1]. Furthermore, the studies of the association between OSA and PCOS were cross-sectional [4, 5, 7], and used surrogate estimates of insulin resistance.

Based upon these observations it seemed reasonable to initiate a pilot, placebo-controlled study in insulin resistant patients with untreated OSA to evaluate the ability of enhanced insulin sensitivity to improve sleep measures, using specific methodology to quantify insulin action and sleep measures. Weight loss can improve insulin sensitivity [8, 9], but even moderate weight loss in overweight/obese patients with OSA is associated with improved sleep measures [9]. Consequently, we chose to administer pioglitazone to insulin resistant patients with OSA; an intervention shown to be more effective than weight loss in improving insulin resistance [8].

Methods

This was a single-blind, randomized, placebo-controlled study to evaluate the effect of pioglitazone on sleep measures in insulin resistant, patients with untreated OSA. Informed consent was obtained from all participants, and the Stanford Administrative Panels for the Protection of Human Subjects approved the protocol. Participants were overweight/ obese (BMI 25.0 – 40.0 kg/m²) men and women (aged 30 – 70 years old), recruited between July 2010 and March 2014. Local print, online, and radio advertisements solicited volunteers with symptoms of OSA, without a prior diagnosis. Additional participants with recent diagnoses of OSA were recruited from the Stanford Sleep Medicine Center. Individuals with histories of type 2 diabetes (or use of antidiabetic drugs), cardiovascular, kidney or liver diseases, or prior treatment for OSA were excluded.

All subjects were provided ad libitum sleep opportunity during full-night in-laboratory PSG at the Stanford Sleep Medicine Center according to standard procedures [10]. OSA was defined by an apnea-hypopnea index (AHI) ≥ 5 events/hour in addition to characteristic symptoms. PSGs were scored manually by a single experienced certified technologist in

accordance to the American Academy of Sleep Medicine Manual (2007) [10]. Minimum AHI ≥ 9 events/hr was required for study enrollment. Severity of OSA was defined as follows: (1) mild: AHI 5 – 14.9 events/ hour; (2) moderate: AHI 15 – 30 events/ hour; and (3) severe: AHI > 30 events/ hour. Other measurements included minimum oxygen saturation, mean oxygen saturation, oxygen desaturation index (defined as the number of times per hour that O_2 sat drops $\geq 3\%$ from baseline), and duration of sleep stage (expressed as percentage of total sleep time). Disease-specific quality of life was evaluated by the short version of the Functional Outcomes of Sleep Questionnaire (FOSQ-10) [11].

Insulin-mediated glucose uptake was quantified directly by a modification [12] of the insulin suppression test [13]. After fasting 12 hours, volunteers received an intravenous infusion of octreotide ($0.27 \mu\text{g}/\text{m}^2/\text{min}$), insulin ($32 \text{ mU}/\text{m}^2/\text{min}$), and glucose ($267 \text{ mg}/\text{m}^2/\text{min}$) over 180 minutes. During the final 30 minutes of the infusion, blood was drawn at 10-minute intervals for measurements of plasma insulin and glucose concentrations and averaged to obtain steady-state plasma insulin and steady-state plasma glucose (SSPG) concentrations. Steady-state plasma insulin concentrations are essentially similar in all individuals, and the SSPG concentration provides a direct measure of insulin-mediated glucose disposal. The higher the SSPG concentration, the more insulin resistant the person, and these estimates of insulin resistance are highly correlated with values obtained with the hyperinsulinemic, euglycemic clamp ($r \sim -0.9$) [14, 15]. Based on outcome data from prior prospective studies, insulin resistance was defined as an SSPG concentration $\geq 150 \text{ mg}/\text{dl}$ ($8.3 \text{ mmol}/\text{l}$), a value shown to predict incident cardio-metabolic diseases [16].

Volunteers who met the above criteria were block randomized 2:1 (pioglitazone:placebo) by sex and BMI (< 32.0 and $\geq 32.0 \text{ kg}/\text{m}^2$). Individuals received pioglitazone $30 \text{ mg}/\text{day}$ for 2 weeks, increased to 45 mg daily for the remaining 6 weeks. Although investigators were aware of treatment assignment, participants, nurses, and sleep technologists were blinded. At biweekly visits, vital signs and weight were obtained, participants monitored for side effects, and advised not to alter their usual diet and physical activity level. Adherence to study drug was assessed by participant report and pill count. Baseline measurements were repeated after the 8-week intervention period. Treatment with continuous positive airway pressure was not permitted for the study duration.

The primary outcome measure was change in AHI. With a sample size of 30 participants assigned to pioglitazone and 15 to placebo, we had 80% power to detect a 50% difference in AHI. Based on continuous positive airway pressure titration guidelines for treatment of OSA [17], a 50% difference in AHI was taken to be clinically meaningful. Statistical analyses were performed using IBM SPSS Statistics 22.0 (Armonk, NY). Data are reported as mean $\pm$ SD, mean $\pm$ SEM, or median [interquartile range]. Paired (follow-up vs. baseline) and unpaired group comparisons were performed by Student's *t* tests for variables that were normally distributed, and the Wilcoxon signed-rank test and Mann-Whitney U test for variables that were not normally distributed. $P < 0.05$ denoted statistical significance and hypothesis testing was two-tailed.

Results

Forty-six participants were initially randomized to pioglitazone (n=31) or placebo (n=15). One individual withdrew from the pioglitazone group for personal reasons. Therefore, 45 participants (30 pioglitazone and 15 placebo) completed the study and were included in the analysis.

Table 1 compares demographic, metabolic, and sleep characteristics in the two groups. The population was overweight/obese, insulin-resistant, and >80% had moderate or severe OSA. Individuals who received pioglitazone gained an average of 0.94 ± 2.0 kg ($p=0.01$) as compared to no weight change in the placebo group. Insulin resistance improved substantially in pioglitazone-treated individuals, with a 31% fall in SSPG concentrations as compared to no change in those receiving placebo ($p<0.001$ for between-group difference) (Supplementary Figure 1). The improvement in insulin sensitivity was accompanied by a decrease in proportion of prediabetes (fasting plasma glucose ≥ 5.56 mmol/l) among individuals pre- vs. post-pioglitazone (70 vs. 43%, $p=0.01$), as compared to no change in individuals pre- vs. post-placebo (73 vs. 60%, $p=0.32$). Pioglitazone administration was not associated with change in FOSQ scores (15.5 ± 3 vs. 14.9 ± 3 ; $p=0.34$).

Results of treatment-associated changes in sleep measures are summarized in Table 2, and demonstrate that there were no statistically significant group differences in sleep variables, with the exception of an increase in total sleep time in placebo-treated patients. Furthermore, the degree of change in SSPG in the pioglitazone arm was not correlated with change in AHI or any other sleep measures (data not shown). Side effects were uncommon in both groups. Two individuals experienced excessive weight gain of 3-4 kg after a dose increase to pioglitazone 45 mg; their doses were lowered to the 30 mg dose.

Discussion

The goal of our study was to see if enhanced insulin sensitivity would improve sleep measures in individuals with untreated OSA. Although treatment with pioglitazone significantly decreased insulin resistance, it did not alter any sleep measures associated with OSA. These findings do not support the presence of a major contributory role for insulin resistance in the pathogenesis of OSA.

We are unaware of an interventional study to test the role of insulin resistance in the pathophysiology of OSA, approaching this question directly by evaluating whether decreasing insulin resistance (in the absence of weight loss) could ameliorate OSA sleep measures. As such our findings differ from prior studies by virtue of being interventional, not cross-sectional or population-based, and using specific methods to quantify both insulin action and sleep measures.

Although our findings do not support the hypothesis that insulin resistance is causal in the development of OSA, possibly the magnitude of the improvement in insulin action and/or duration of study treatment were insufficient to result in any improvement in sleep measures. Second, although pioglitazone is an effective insulin-sensitizer, it binds to a nuclear receptor and has been shown to modulate a number of other actions, not all of which are beneficial

[18]. Consequently, an unrecognized adverse effect of pioglitazone could have obviated a beneficial effect of enhanced insulin sensitivity on OSA-related sleep measures. These issues could be addressed by evaluating the ability of weight loss to improve both insulin sensitivity and sleep measures in OSA, but such a study would be confounded by the need to distinguish between the effect of weight loss *per se* vs. a weight-loss associated improvement in insulin sensitivity on OSA severity and symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This research was funded by NIH grants 5K23 DK088877, NHLBI MapGen 5U01 HL108647, and supported by Human Health Service grant M01-RR00070. This work was supported through a Patient-Centered Outcomes Research Institute (PCORI) Pilot Project Program Award (CE-12-11-4137) Sustainable Methods, Algorithms, and Research Tools for Delivering Optimal Care Study (PI: Kushida). All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Abbreviations

AHI	apnea-hypopnea index
OSA	obstructive sleep apnea
SSPG	steady-state plasma glucose

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Highlights

- Pioglitazone substantially improved insulin sensitivity in insulin-resistant patients with untreated OSA.
- Enhanced insulin sensitivity was not associated with improvement in sleep measurements.
- Insulin resistance does not appear to be causal in the pathogenesis of OSA.

Table 1

Baseline characteristics of patients with OSA.

	Pioglitazone (n=30)	Placebo (n=15)	<i>p</i> value
Age (years)	51 ± 11	50 ± 12	0.99
Female, <i>n</i> (%)	10 (33)	5 (33)	1.0
Non-Hispanic white, <i>n</i> (%)	16 (53)	11 (73)	0.20
Waist circumference (cm)	106 ± 10	107 ± 10	0.79
BMI (kg/m ²)	31.8 ± 3.5	31.3 ± 2.7	0.66
Fasting glucose (mmol/L)	5.8 ± 0.5	5.8 ± 0.5	0.92
Impaired fasting glucose, <i>n</i> (%)	21 (70)	9 (60)	0.82
Steady-state plasma glucose (mmol/L)	11.9 ± 2.1	12.3 ± 2.0	0.56
Steady-state plasma insulin (pmol/L)	501 ± 214	520 ± 121	0.80
Systolic blood pressure (mm Hg)	126 ± 13	133 ± 17	0.14
Diastolic blood pressure (mm Hg)	80 ± 8	85 ± 8	0.046
Apnea-hypopnea index (events/hr)	36.9 ± 24	40.8 ± 26	0.63
OSA severity (mild/ moderate/ severe, %)	5 (17)/ 10 (33)/ 15 (50)	3 (20)/ 3 (20)/ 9 (60)	0.65

Data are mean ± SD unless otherwise indicated.

Table 2

Changes in sleep measures during overnight polysomnography in the pioglitazone and placebo groups.

	Pioglitazone (n=30)				Placebo (n=15)			
	Baseline	8 weeks	Within-group difference (95%CI)	p	Baseline	8 weeks	Within-group difference (95% CI)	Between-group difference p
Apnea-hypopnea index (events/hr)	30.6 [17-52]	35.8 (21-49]	4.0 (-3.3 to 11.2)	0.32	33.9 [17-69]	34.4 [18-47]	-6.7 (-14.5 to 1.0)	0.11
REM-AHI (events/hr)	44.0 [23-69]	45.7 [27-59]	0.02 (-6.1 to 6.2)	0.88	46.6 [28-69]	38.4 [24-68]	-3.2 [-17.5 to 11]	0.87
NREM-AHI (events/hr)	31.3 [11-52]	34.3 [17-48]	5.0 (-3.3 to 13.4)	0.38	30.2 [14-69]	36.6 [16-44]	-6.4 (-15.6 to 2.8)	0.14
Minimum O ₂ sat (%)	84 [78-88]	85 [77-90]	0.8 (-1.4 to 3.0)	0.51	83 [79-87]	82 [79-88]	-0.8 (-2.6 to 1.0)	0.42
Mean O ₂ sat (%)	95 [93-97]	95 [93-97]	0.2 (-0.2 to 0.7)	0.17	94 [93-96]	95 [94-96]	0.5 (-0.002 to 0.01)	0.18
Oxygen Desaturation Index (events/hr)	10.4 [4-27]	9.4 [3-23]	1.1 (-4.8 to 6.9)	0.98	13.9 [3-22]	12.3 [5-27]	2.5 (-3.0 to 8.0)	0.56
N1 duration (%)	2.9 [1.9-8.3]	2.3 [1.3-5.2]	-1.1 (-3.7 to 1.4)	0.11	3.2 [1.0-9.2]	2.5 [1.0-4.7]	-1.7 (-3.9 to 0.6)	0.17
N2 duration (%)	50 [39-59]	47.7 [40-59]	0.6 (-4.3 to 5.4)	0.36	43.9 [37-64]	48.6 [45-54]	2.1 (-5.1 to 9.2)	0.57
N3 duration (%)	24.3 [13-34]	26.4 [13-35]	-1.1 (-5.2 to 3.0)	0.86	28.2 [11-37]	28.7 [16-37]	-0.1 (-5.3 to 5.1)	0.91
REM duration (%)	21.6 [18-24]	22.2 [17-27]	0.6 (-2.6 to 3.8)	0.48	19.5 [15-26]	22.2 [14-26]	-0.2 (-6.2 to 5.7)	0.96
Sleep onset latency (min)	13 [8-23]	9 [4-21]	-5 (-22 to 11)	0.42	18 [10-40]	12 [7-19]	-19 (-36 to -2)	0.03
REM latency (min)	108 [80-163]	86 [67-166]	-4 (-33 to 24)	0.75	119 [97-163]	122 [77-288]	39 (-39 to 116)	0.53
N3 latency (min)	16 [9-27]	14 [7-27]	-3 (-29 to 24)	0.62	24 [19-60]	17 [11-24]	-0.1 (-30 to 29)	0.19
Wake after sleep onset (min)	89 [56-127]	76 [51-119]	-12 (-30 to 6)	0.27	76 [54-149]	82 [54-155]	1.5 (-27 to 30)	0.83

Pioglitazone (n=30)						Placebo (n=15)			
	Baseline	8 weeks	Within-group difference (95% CI)	p	Baseline	8 weeks	Within-group difference (95% CI)	p	Between-group difference p
Total sleep time (min)	364 [314-397]	357 [297-407]	4.4 (−26 to 35)	0.94	336 [262-360]	367 [286-396]	42 (16 to 69)	0.005	0.05

Data are median [interquartile range] unless otherwise specified. Duration of sleep stages expressed as percentage of total sleep time. REM-AHI, AHI during REM sleep; NREM-AHI, AHI during non-REM sleep.