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Effect of Pioglitazone on Cardio-Metabolic Risk in Patients with Obstructive Sleep Apnea

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Abstract

Prevalence of insulin resistance is increased in patients with obstructive sleep apnea (OSA). Since insulin resistance is an independent predictor of cardiovascular disease (CVD), this study was initiated to see if pioglitazone administration would improve insulin sensitivity, and thereby decrease risk of CVD in overweight/obese, nondiabetic, insulin-resistant patients with untreated OSA. Patients (n=30) were administered pioglitazone (45 mg/day) for 8 weeks, and measurements were made before and after intervention of insulin action (insulin-mediated glucose uptake by the insulin suppression test), C-reactive protein, lipid/lipoprotein profile, and gene expression profile of peri-umbilical subcutaneous fat tissue. Insulin sensitivity increased 31% ($p<0.001$) among pioglitazone-treated individuals, associated with a decrease in C-reactive protein concentration ($p=0.001$), a decrease in plasma triglyceride and increase in high-density lipoprotein cholesterol concentrations ($p=0.001$), accompanied by significant changes in apolipoprotein A1 and B concentrations and lipoprotein subclasses known to decrease CVD risk. In addition, subcutaneous adipose tissue gene expression profile showed a 1.6-fold ($p<0.01$) increase in GLUT4 expression, as well as decreased expression in 5 of 9 inflammatory genes ($p<0.05$). In conclusion, enhanced insulin sensitivity can significantly decrease multiple cardio-metabolic risk factors in patients with untreated OSA, consistent with the view that coexisting insulin resistance plays an important role in the association between OSA and increased risk of CVD.

Keywords

Obstructive sleep apnea; cardio-metabolic risk; insulin resistance; pioglitazone; lipoproteins

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Introduction

There is evidence that insulin resistance is increased in patients with obstructive sleep apnea (OSA), and manipulation of OSA-related sleep variables (e.g. hypoxia, short sleep) decreases insulin sensitivity in healthy individuals.^{1,2} These observations have led to the view that sleep disturbances, including OSA, are independent risk factors for the development and exacerbation of insulin resistance.³ Risk of cardiovascular disease (CVD) is also enhanced in patients with OSA.^{4,5} Since insulin resistance, *per se*, is an independent predictor of CVD,^{6,7} it can be argued that OSA-induced insulin resistance contributes to increased prevalence of CVD in these patients. As a corollary it could be hypothesized that enhancing insulin sensitivity in overweight/obese, insulin-resistant patients, not being treated for OSA, would lead to an improvement in cardio-metabolic risk profile. To test this hypothesis, we administered pioglitazone, a drug which decreases insulin resistance,⁸ to overweight/obese, nondiabetic individuals with untreated OSA, screened to be insulin-resistant. The goals of the study were to see if: 1) pioglitazone treatment would enhance insulin sensitivity in insulin-resistant patients with untreated OSA; and 2) if so, would the increase in insulin sensitivity lead to an improvement in cardio-metabolic profile and associated CVD risk.

Methods

Overweight/obese (BMI 25.0 – 40.0 kg/m²) men and women (30 – 70 years old) volunteered for these studies performed at Stanford Medical Center between 2010 and 2014. They were identified by their response to local advertisements soliciting volunteers with symptoms of OSA, as well by being recently diagnosed with OSA at the Stanford Sleep Medicine Center. Individuals with CVD, diabetes (or use of antidiabetic drugs), kidney, liver diseases, or prior therapy for OSA were excluded. Informed consent was obtained from all participants, and the Stanford Institutional Review Board approved the protocol. The results of studies on the effect of pioglitazone on sleep parameters in patients with untreated OSA have been published,⁹ and demonstrated that treatment with pioglitazone did not alter sleep measures associated with OSA.

Full-night in-laboratory polysomnography was performed in all participants at the Stanford Sleep Medicine Center according to standard procedures prior to enrollment in the study. A single experienced certified sleep technologist manually scored these observations in accordance with the American Academy of Sleep Medicine Manual (2007).¹⁰ Volunteers who had a minimum apnea-hypopnea index (AHI) > 9 events/hr were eligible for participation in the study. Severity of OSA 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. Patients did not receive any treatment for OSA (including continuous positive airway pressure (CPAP)) for the study duration.

The presence of insulin resistance was based on the specific measurement of insulin-mediated glucose uptake by the modified¹¹ insulin suppression test.¹² After fasting overnight, volunteers received intravenous octreotide (0.27 mcg/m²/min), insulin (32 mU/m²/min), and glucose (267 mg/m²/min) over 180 minutes. During the final 30 minutes

blood was drawn every 10 minutes for plasma insulin and glucose measurements, and averaged to obtain a mean steady-state plasma insulin and steady-state plasma glucose (SSPG) concentrations. Under these conditions steady-state plasma insulin concentrations are similar in all individuals, and the SSPG concentration provides a direct measure of insulin's ability to mediate disposal of the infused glucose load. Higher SSPG concentrations reflect greater insulin resistance. Insulin sensitivity, thus quantified, is highly correlated with values obtained with the hyperinsulinemic, euglycemic clamp ($r \sim 0.9$).^{13,14} Based on outcome data from prior prospective studies, insulin resistance was defined as an SSPG concentration > 150 mg/dL, a value shown to predict incident cardio-metabolic diseases.^{6,7}

Qualified volunteers underwent lipid/lipoprotein profiles obtained by analyzing overnight fasting plasma samples with the Vertical Auto Profile method.^{15,16} This approach provides a direct measure of cholesterol concentrations in high-density, low-density, very-low-density, intermediate-density lipoproteins, and lipoprotein (a), subclasses of high-, low-, intermediate-, and very low density lipoprotein, low-density lipoprotein diameter, and calculates concentrations of apolipoproteins B and A1. These samples were also used to measure high sensitivity C-reactive protein (hsCRP).

A subset of participants ($n=28$) underwent abdominal subcutaneous adipose tissue biopsies under sterile conditions after administration of local anesthesia (0.25% bupivacaine with 1:200,000 epinephrine) in a region lateral to the umbilicus. Aspirated tissue was weighed and placed in liquid nitrogen and stored at -80° until used to determine the gene expression profile. Total RNA was extracted from the subcutaneous adipose tissue using Trizol® (Ambion, Carlsbad, CA, USA). cDNA was synthesized from total RNA using the High-Capacity RNA-to-cDNA™ Kit (Applied Biosystems, Foster City, CA, USA). Taqman primer/probe sets for mRNA transcripts of the following were purchased from Applied Biosystems (Foster City, CA, USA): peroxisome proliferator activated receptor γ 1/2 (PPAR γ 1/2), adiponectin, leptin, sterol receptor element binding protein 1c (SREBP1c), GLUT4, CD68, IL-6, IL-8, monocyte chemotactic protein-1 (MCP-1), TNF- α , TNF- α receptor 1, plasminogen activator inhibitor-1 (PAI-1), CD45, YKL-40, and 18S ribosomal RNA as a control probe. Amplification was carried out in triplicate on an ABI Prism 7700 sequence detection system at 50°C for 2 min and 95°C for 10 min, followed by 40 cycles of 95°C for 15 s and 60°C for 1 min. A threshold cycle (C_t value) was obtained from each amplification curve, and a C_t value was first calculated by subtracting the C_t value for 18S ribosomal RNA from the C_t value for each sample. A C_t value was calculated by subtracting the C_t value of a baseline SAT sample chosen arbitrarily (control). Fold changes compared with the control were then determined by calculating 2^{-C_t} .

Upon completion of the baseline procedures, participants received pioglitazone 30 mg/day for 2 weeks, which was then increased to 45 mg daily for the remainder of the study. At biweekly visits, vital signs and weight were obtained, participants monitored for side effects, and encouraged to maintain their usual diet and physical activity level.

Statistical analyses were performed using IBM SPSS Statistics 22.0 (Armonk, NY). Paired (follow-up vs. baseline) were performed by Student's t tests and the Wilcoxon signed-rank test. $P < 0.05$ denoted statistical significance and all hypothesis testing was two-tailed.

Results

Table 1 describes demographic, metabolic, and sleep characteristics in the experimental population. Participants were overweight/obese, insulin-resistant, and >80% had moderate or severe OSA. Seventy percent had prediabetes based on fasting glucose concentrations. Six patients were taking anti-hypertensive medications, 4 individuals were taking statins, and 1 individual was taking a fibrate prior to study enrollment. These medications were not adjusted during the study by study personnel.

The results illustrated in Fig. 1 (a) demonstrate that obese/overweight, insulin-resistant patients with untreated OSA became significantly more insulin sensitive, with a 31% decrease in SSPG concentration ($p < 0.001$), when treated with pioglitazone. The improvement in insulin sensitivity occurred in the context of a mean 0.94 kg weight gain ($p = 0.01$) (Table 2). In addition, Fig. 1 (b) also shows that hsCRP concentrations declined in association with the improvement in insulin sensitivity ($p = 0.01$).

The impact of the treatment on changes in metabolic and lipoprotein concentrations is summarized in Table 2, and demonstrates that pioglitazone-treated patients underwent a significant shift to a less atherogenic lipid profile. Plasma triglyceride concentrations decreased and high-density lipoprotein cholesterol concentration decreased, associated with a significant change in small, dense low-density lipoprotein pattern (a decrease in Pattern B and an increase in pattern A). In addition, concentrations of apolipoprotein B decreased and apolipoprotein A-1 increased in pioglitazone-treated patients.

The change in the subcutaneous fat expression of genes related to insulin action, cell differentiation, and inflammation are presented in Figure 2. Treatment with pioglitazone led to a 1.6-fold ($p < 0.01$) increase in GLUT4 expression, as well as decreased expression in 5 of 9 inflammatory genes ($p < 0.05$).

Discussion

The current study was based on the hypothesis that the coexistence of insulin resistance in patients with OSA plays a significant role in the increased incidence of cardio-metabolic risk in these patients. The results demonstrate that overweight/obese, insulin-resistant, patients with untreated OSA became significantly more insulin sensitive when treated with pioglitazone, associated with a substantial improvement in multiple risk factors related to CVD. The increase in insulin sensitivity was demonstrated at both the physiological level (lower SSPG concentrations) and transcriptional level (increased SAT GLUT4 gene expression). These improvements translated to an attenuation of CVD risk factors associated with insulin resistance.^{17–19} Specifically, plasma C-reactive protein concentrations declined, as did the expression in subcutaneous fat tissue of several inflammatory genes. In addition, plasma concentrations of triglyceride were lower and high-density lipoprotein cholesterol higher when patients were administered pioglitazone, in association with changes in

concentrations of apolipoproteins and several lipoprotein particle subclasses that significantly decreased the atherogenicity of the lipid/lipoprotein profile of these overweight/obese, insulin-resistant patients with untreated OSA.

The implications of this study's findings can be discussed at two levels. At the conceptual level it provides information relevant to the relationships among OSA, insulin resistance and cardio-metabolic disease. The fact that the enhanced insulin sensitivity and decreased cardio-metabolic risk occurred in the absence of weight loss or CPAP treatment raises the possibility that the association between OSA and increased cardio-metabolic risk is mediated to a significant degree by insulin resistance in these patients, and not simply a consequence of OSA, *per se*. As such, from a pragmatic perspective one may extrapolate that if we are to lower CVD risk in patients with OSA, targeting insulin resistance would be a sensible approach.

Secondly, the fact that the enhanced insulin sensitivity and decreased cardio-metabolic risk occurred in the absence of CPAP intervention has relevance to questions raised regarding the ability of CPAP to decrease risk of cardio-metabolic disease. For example, in a systematic analysis of randomized studies comparing therapeutic vs. sham CPAP intervention,²⁰ the authors concluded that a decrease in sympathetic activity was the only cardio-metabolic risk factor that improved with CPAP use. In contrast, "CPAP did not change glucose, lipids, insulin resistance levels, or the ratio of patients with the metabolic syndrome." The benefits of CPAP on lowering blood pressure have been more consistent,^{21,22} but CPAP use did not reduce incident hypertension or cardiovascular events in nonsleepy patients with OSA.²³ Recently, in a large secondary prevention trial, CPAP treatment did not prevent cardiovascular events in patients with moderate-to-severe OSA and histories of CVD.²⁴ Variable patient adherence to CPAP²⁵ may limit the efficacy of CPAP treatment in reducing cardio-metabolic risk. Nonetheless, these observations suggest that CPAP may be insufficient to reduce cardio-metabolic risk, and that separate interventions to target these risk factors are warranted.

Although prevalence of overweight/obesity is increased in patients with OSA,²⁶ we chose not to implement a weight loss intervention as the means to enhance insulin sensitivity. The rationale is that weight loss has been documented to ameliorate OSA severity in clinical trials,²⁷ and weight loss, itself, can improve insulin sensitivity and other cardio-metabolic risk factors.¹⁸ Consequently, it would be difficult—if not impossible—to determine if improvement in cardio-metabolic risk profile is secondary to clinical improvement in OSA in response to a reduction in adiposity or due to an increase in insulin sensitivity.

Given the results of this study, it seems reasonable to suggest that efforts to enhance insulin sensitivity be implemented in overweight/obese patients with OSA displaying the cardio-metabolic risk factors associated with insulin resistance. Whether these changes would translate to cardiovascular benefit is uncertain, but there is some data to support that pioglitazone may have favorable effects on atherosclerosis in prediabetes, independent of lipids, glucose, and inflammatory markers.²⁸ That said, in view of concerns over potential side-effects of long-term use of thiazolidinedione compounds,^{29,30} accomplishing this goal by initiating chronic treatment with pioglitazone may be less than ideal. However, since

weight loss should help both sleep measures *and* insulin resistance in patients with OSA, more aggressive efforts at weight loss would seem to be indicated in overweight/obese, insulin-resistant patients with OSA. Unfortunately, at this time there is not abundant understanding of how effective these efforts can be in this population, and we encourage implementation of studies that would provide this crucial information. Nonetheless, based upon the results of this study, and given concern that CPAP may be insufficient to substantially reduce cardio-metabolic risk, we suggest that additional interventions should be considered to decrease cardio-metabolic risk in insulin-resistant patients with OSA.

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Figure 1.

Change in (a) insulin sensitivity as quantified by steady-state plasma glucose (SSPG) concentrations and (b) high sensitivity C-reactive protein (hsCRP) before and after pioglitazone (n=30).

Figure 2.

Subcutaneous adipose tissue gene expression of individuals before and after pioglitazone (n=28) treatment. Data expressed as mean ± SEM. ** $P < 0.01$, * $P < 0.05$.

Table 1

Patient characteristics

	Age	Sex	BMI (kg/m ²)	Fasting glucose (mg/dL)	Steady-state plasma glucose (mg/dL)	Apnea-hypopnea index (events/hr)
1	30	Male	31.4	98	213	12.9
2	32	Male	35.6	100	220	21.6
3	33	Female	28.2	95	290	9.0
4	33	Male	29.8	89	207	15.5
5	36	Male	28.9	104	158	16.9
6	38	Female	25.7	112	181	26.4
7	38	Male	27.5	96	226	8.9
8	42	Female	37.0	93	249	44
9	45	Male	27.4	100	181	24.7
10	45	Male	37.9	108	227	53.3
11	48	Female	27.4	114	229	11.8
12	48	Male	36.4	101	183	17.0
13	49	Female	35.7	104	162	104.2
14	50	Female	28.6	91	270	21.5
15	52	Male	33.2	111	216	63.4
16	54	Male	32.1	120	270	35.3
17	54	Male	37.6	108	242	34.8
18	55	Male	28.1	115	157	72
19	56	Male	30.8	98	246	71.9
20	56	Female	33.6	109	217	14.8
21	58	Female	30.8	102	203	15.5
22	58	Male	32.8	94	210	42.9
23	59	Male	32.1	104	165	45.2
24	60	Male	30.0	118	220	45.6
25	60	Male	30.3	123	274	51.5
26	61	Female	35.6	93	160	20.3
27	64	Female	33.6	110	241	76.1
28	65	Male	35.5	106	217	17.6

	Age	Sex	BMI (kg/m ²)	Fasting glucose (mg/dL)	Steady-state plasma glucose (mg/dL)	Apnea-hypopnea index (events/hr)
29	68	Male	29.3	120	173	49.9
30	68	Male	30.3	105	218	61.9

Table 2

Changes in metabolic and lipoprotein concentrations in insulin-resistant individuals with untreated OSA receiving pioglitazone for 8 weeks (n=30)

Variable	Baseline	8 weeks	Within-group difference (95%CI)	p
Weight (kg)	92.4 ± 15	93.4 ± 15	0.94 (0.2 to 1.7)	0.01
Waist circumference (cm)	106 ± 10	105 ± 19	-0.7 (-6.4 to 5.1)	0.81
Body mass index (kg/m ²)	31.8 ± 3.5	32.2 ± 3.5	0.4 (0.2 to 0.7)	0.001
Fasting glucose (mg/dL)	105 ± 9	100 ± 8	-4.77 (-8 to 2)	0.002
Total cholesterol (mg/dL)	191 ± 49	189 ± 46	-1.9 (-12 to 9)	0.72
Total LDL (mg/dL)	120 ± 41	116 ± 41	-3.5 (-11 to 4)	0.37
LDL ₁ (mg/dL)	17 ± 8	19 ± 8	1.5 (-0.7 to 3.6)	0.18
LDL ₂ (mg/dL)	20 ± 17	30 ± 17	10 (4.9 to 16)	<0.001
LDL ₃ (mg/dL)	45 ± 18	40 ± 18	-0.05 (-0.1 to 0.01)	0.09
LDL ₄ (mg/dL)	17 ± 14	8 ± 9	-9 (-13 to -5)	0.001
IDL (mg/dL)	15 ± 8	15 ± 6	-0.7 (-2.3 to 1.0)	0.42
Total VLDL (mg/dL)	27 ± 10	24 ± 7	-3.1 (-5.9 to -0.3)	0.03
VLDL ₁₊₂ (mg/dL)	12 ± 6	11 ± 4	-1.8 (-3.6 to -0.1)	0.04
VLDL ₃ (mg/dL)	14 ± 4	13 ± 4	-1.1 (-2.3 to 0.1)	0.07
Triglycerides (mg/dL)	158 ± 62	128 ± 53	-30 (-45 to -15)	<0.001
HDL cholesterol (mg/dL)	45 ± 11	49 ± 11	4.8 (2.2 to 7.3)	0.001
HDL ₂ cholesterol (mg/dL)	10 ± 5	12 ± 5	1.7 (0.7 to 2.7)	0.002
HDL ₃ cholesterol (mg/dL)	34 ± 7	38 ± 7	3.2 (1.5 to 5.0)	0.001
Lp(a) (mg/dL)	5.9 ± 5	6.2 ± 4	0.3 (-1.3 to 1.9)	0.37
LDL density pattern A/AB/B (n)	13/2/15	24/3/3	N/A	<0.001
Apolipoprotein B (mg/dL)	100 ± 26	95 ± 23	-5.3 (-10 to -0.1)	0.045
Apolipoprotein A1 (mg/dL)	139 ± 18	147 ± 19	7.8 (3 to 13)	0.004
Apolipoprotein B/Apolipoprotein A1 ratio	0.72 ± 0.2	0.65 ± 0.2	-0.07 (-0.1 to -0.04)	<0.001
High sensitivity C-reactive protein (mg/L)	2.8 ± 2	2.2 ± 2	-0.6 (-1.1 to -0.1)	0.01

Data are expressed as mean ± SD.

HDL = high density lipoprotein; iDL = intermediate density lipoprotein; LDL= low density lipoprotein; VLDL = very low density lipoprotein

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