ATS 2013 INTERNATIONAL CONFERENCE May 17 - May 22 Philadelphia
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News Release

FOR RELEASE May 19, 2013, 4:45 p.m. EST

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Session B19: Mini Symposium - Oral Presentation
Monday, May 20, 2013, 8:15 am. – 10:45 a.m.
Location: Room 204 A-B (200 Level) Pennsylvania Convention Center

PRESS CONFERENCE: Sunday, May 19, 4:45 p.m., Room 110A (Level 100), Pennsylvania Convention Center

Treatment of Sleep Apnea Improves Glucose Levels in Prediabetes

ATS 2013, PHILADELPHIA – Optimal treatment of sleep apnea in patients with prediabetes improves blood sugar (glucose) levels and thus can reduce cardiometabolic risk, according to a study to be presented at the ATS 2013 International Conference in Philadelphia.

"Sleep apnea, a condition associated with breathing disturbances during sleep is known to be associated with abnormalities in glucose metabolism, but whether treatment of sleep apnea has any beneficial effects on glucose metabolism is still under investigation" said lead author Sushmita Pamidi, MD, of the Department of Medicine at McGill University in Montreal, Canada-"We have studied patients with sleep apnea and prediabetes, a condition defined as higher than normal blood glucose levels but not high enough to be considered diabetes. We found that optimal treatment of sleep apnea with continuous positive airway pressure (CPAP) for two weeks led to significant improvements in glucose levels following an oral glucose challenge without affecting insulin secretion, suggesting an improvement in insulin sensitivity."

Insulin is a hormone produced in the pancreas that regulates the metabolism of glucose in the body. Insulin resistance is a condition in which normal amounts of insulin are not adequate to produce a normal cellular insulin response to glucose ingestion. Low insulin sensitivity, a measure of how sensitive a person's body is to the effects of insulin, is associated with the development of type 2 diabetes.

As many as two-thirds of type 2 diabetic patients may be suffering from unrecognized sleep apnea . The main treatment option for sleep apnea is CPAP, in which a machine delivers air at a specific pressure via a breathing tube connected to a facemask in order to splint the upper airway open and prevent further breathing disturbances during sleep. The breathing disturbances during sleep that result in sleep apnea have been linked to prediabetic conditions such as insulin resistance and glucose intolerance as well as type 2 diabetes and cardiovascular complications.

The current study included 39 adults with sleep apnea and prediabetes who were randomized to two weeks of either CPAP treatment or placebo tablet. Before and after the treatment period, study participants underwent an oral glucose tolerance test, a test that measures body's ability to use glucose. A unique aspect of the study is that subjects slept each night in the research laboratory, ensuring optimal adherence to CPAP treatment. Glucose tolerance, insulin secretion, and insulin sensitivity, all markers for the risk of diabetes, were measured Subjects were also monitored for the quantity and quality of sleep, 24 hour blood pressure, heart rate, weight, energy expenditure and hormones affecting diabetes risk.

"Effective treatment of OSA is known to have a positive impact on a number of important health outcomes and in our study we observed beneficial effects on glucose metabolism," said principal investigator, Esra Tasali, MD, assistant professor of pulmonary and critical care medicine at the University of Chicago. This "proof of concept" study may provide essential information for designing larger multicenter clinical trials that will determine whether CPAP treatment could be a first line intervention to prevent or delay the development of type 2 diabetes. Our study adds to the current literature by demonstrating that CPAP treatment of sleep apnea in patients at risk for developing diabetes may lower this risk, and an assessment for sleep apnea may be appropriate as part of the clinical evaluation of patients with prediabetes," said Dr. Pamidi.

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** Please note that numbers in this release may differ slightly from those in the abstract. Many of these investigations are ongoing; the release represents the most up-to-date data available at press time.*

Abstract 39588

Effective Treatment Of Obstructive Sleep Apnea Improves Glucose Tolerance In Prediabetes: A Randomized Placebo-Controlled Study

Type:	Scientific Abstract
Category:	16.02 - Sleep Disordered Breathing: Cardiovascular and Neuroendocrine Interactions (SRN)
Authors:	S. Pamidi[1], M. Stepien[2], K. Sharif-Sidi[2], H. Whitmore[2], L. Morselli[2], K. Wroblewski[2], E. Tasali[2]; [1]McGill University - Montreal, QC/CA, [2]University of Chicago - Chicago/US

Abstract Body

Introduction/Rationale:

Prediabetes is characterized by high glucose levels that are intermediate between normal glucose tolerance and overt diabetes, insulin resistance and abnormalities in insulin secretion. There is overwhelming evidence to support an association between obstructive sleep apnea (OSA) and prediabetic states. However, it remains unclear whether continuous positive airway pressure (CPAP) treatment of OSA can improve glucose metabolism. A major limitation of prior studies is insufficient CPAP use. The aim of this randomized placebo-controlled study is to test the hypothesis that effective CPAP treatment of OSA with optimum adherence during the entire night can improve glucose metabolism in prediabetes and reduce cardiometabolic risk.

Methods:

Adults (age ≥45 years, BMI ≥25 kg/m^2) with prediabetes and OSA (apnea-hypopnea index >5) were recruited from the community. Subjects were randomized in a 2:1 ratio to either 2 weeks of optimal CPAP treatment or oral placebo tablet 30min before bedtime. Both groups spent each night in the laboratory with 8-hour bedtimes. Sleep was recorded by polysomnography and the optimum adherence to CPAP during the entire night was ensured by continuous supervision. Subjects left the laboratory during the daytime to engage in their daily routine activities. At baseline and after each treatment, subjects underwent a morning oral glucose tolerance test (OGTT). Data from an intravenous glucose tolerance test (to estimate insulin sensitivity), 24-hr blood pressure monitoring, and daily measurements of weight, food intake and activity-related energy expenditure were also obtained.

Insulin secretory rates were calculated by the deconvolution method using c-peptide profiles measured during the OGTT. The areas under the glucose and insulin curves, and insulin secretion rates during the OGTT were calculated according to the trapezoidal rule.

Results:

A total of 39 subjects were randomized to either CPAP or placebo tablet. Baseline characteristics were similar between the two groups (**Table 1**). Profiles of glucose, insulin and insulin secretion rates during the OGTT are illustrated in **Figure 1**. The 2-hr glucose levels and incremental area under the glucose curve during the OGTT significantly decreased after CPAP as compared to placebo tablet, whereas insulin levels and insulin secretion rates did not differ between the two groups (**Table 2**).

Conclusions:

In prediabetics, CPAP treatment of OSA with optimal adherence during the entire night results in lower glucose levels without change in insulin secretion, suggesting increased insulin sensitivity following an oral glucose challenge. Effective CPAP treatment of OSA can improve glucose metabolism and thus reduce cardiometabolic risk.

Table 1. Baseline characteristics of study population

Characteristic	CPAP (n=26)	Placebo Tablet (n=13)	P value†
Age, years	53.8 ± 6.2	55.2 ± 8.4	0.72
Body mass index, kg/m^2	36.8 ± 7.8	32.7 ± 4.3	0.13
Male, n (%)	16 (62)	10 (77)	0.48
High ethnicity- based diabetes risk, n (%)	13 (50)	8 (62)	0.50
Family history of diabetes, n (%)	10 (40)	4 (31)	0.58
Apnea-hypopnea index (AHI)	45.2 ± 29.6	40.4 ± 23.1	0.61
Epworth Sleepiness Score	10.0 ± 5.9	10.9 ± 5.0	0.62
Hypertension, n (%)	5 (19)	0 (0)	0.15
Systolic blood pressure, mmHg	133.4 ± 13.1	127.4 ± 8.3	0.14
Diastolic blood pressure, mmHg	80.0 ± 8.2	74.2 ± 6.2	0.03
Dyslipidemia, n (%)	12 (46)	10 (77)	0.31
Total Cholesterol, mg/dL	189.2 ± 28.2	205.5 ± 37.5	0.14
HDL cholesterol, mg/dL	49.7 ± 9.9	51.1 ± 21.2	0.78
LDL cholesterol, mg/dL	116.5 ± 27.6	130.0 ± 34.2	0.19
Triglyceride, mg/dL	115.3 ± 64.3	122.4 ± 82.9	0.77
Hemoglobin A1c, %	5.8 ± 0.4	5.8 ± 0.3	0.90
Fasting glucose, mg/dL	103.9 ± 8.4	101.6 ± 8.7	0.44
2-hour glucose, mg/dL	154.6 ± 22.4	144.9 ± 33.9	0.29
Fasting insulin, pmol/L	74.0 ± 37.5	70.7 ± 32.9	0.81

Data are means ± SD unless otherwise specified. † P values are from two-sided unpaired t-test if the data were normally distributed and Mann-Whitney U test if not for continuous variables, and Chi-square tests for categorical variables except for gender and hypertension (Fisher's exact test).

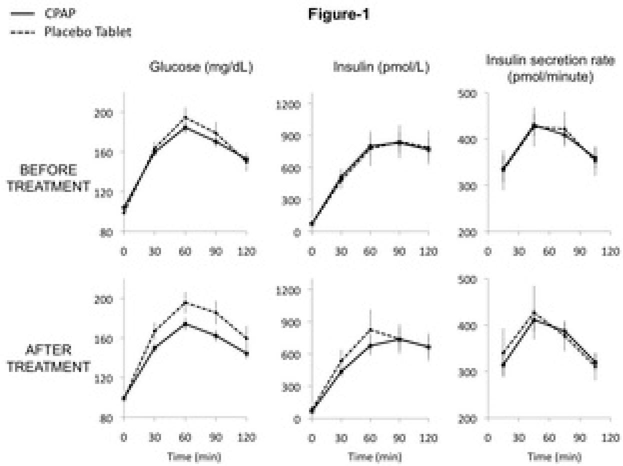
Ethnicity-based diabetes risk was categorized as "high" for African Americans,Hispanics and Asians and "low" for Whites. Family history of diabetes was considered positive if at least one first-degree relative had type 2 diabetes. Dyslipidemia was considered present if any of following were satisfied: prior medical history, any abnormal lipid value, anti-lipid therapy. Hypertension was considered present if any of following were satisfied: prior history of hypertension, anti-hypertensive use, systolic or diastolic blood pressure >140 or > 90 mm Hg respectively.

Table 2: Effects of CPAP and Placebo Tablet on Measures of Glucose Tolerance and Insulin Secretion

	Treatment Effect		Difference (95% CI)	P value†
	CPAP (n=19)	Placebo Tablet (n=10)		
Fasting glucose, mg/dL	-4.8 ± 7.4	0.3 ± 6.3	-5.03 (-10.7 to 0.6)	0.08
2-hr glucose, mg/dL	-8.3 ± 16.9	9.8 ± 19.8	-18.1 (-32.5 to -3.8)	0.02
$incAUC_{glu}$, μU. mL^{-1}. min	-741.2 ± 1292.4	485.5 ± 1755.0	-1226.7 (-2399.4 to -54.0)	0.04
$incAUC_{ins}$, mg. dL^{-1}. min	-1351.2 ± 3434.8	-458.7 ± 1457.8	-892.5 (-3239.7 to 1454.6)	0.40
AUC ISR, pmol/minute	-1073 ± 2020	-675 ± 2029	-399 (-2020 to 1223)	0.62

Data are means ± SD unless otherwise specified. † P values for the difference between CPAP and Placebo Tablet groups are from two-sided unpaired t-test if the data were normally distributed and Mann-Whitney U test if not. Treatment effect was calculated for all variables by subtracting post-treatment value from the pre-treatment value. Difference was calculated for all variables by subtracting Placebo Tablet effect from CPAP effect. Insulin secretory rates were calculated by deconvolution method using c-peptide profiles measured during the oral glucose tolerance test. The incremental areas under the glucose ($incAUC_{glu}$) and insulin ($incAUC_{ins}$) curves and the area under the curve for insulin secretion rate (AUC ISR) were calculated according to the trapezoidal rule between 0 and 120 min during the oral glucose tolerance test.

Figure-1



CPAP
Placebo Tablet
Glucose (mg/dL)
Insulin (pmol/L)
Insulin secretion rate (pmol/minute)
BEFORE TREATMENT
AFTER TREATMENT
Time (min)