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The Effects of Continuous Positive Airway Pressure in Type 2 Diabetic Patients with Newly Diagnosed Obstructive Sleep Apnea

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The Effects of Continuous Positive Airway Pressure in Type 2 Diabetic Patients with Newly Diagnosed Obstructive Sleep Apnea

Abstract

Background: Type 2 diabetes is a major epidemic in the United States, with an estimated 23.6 million diabetics or 7.8% of the population according to the National Diabetic Information Clearinghouse. Obstructive Sleep Apnea is also a major epidemic affecting 4-17% of the population. Each of these disorders, independently, can lead to increased morbidity and mortality. Rapidly developing research suggests these disorders share many important factors that must be investigated further.

Purpose of Study: To determine if continuous positive airway pressure (CPAP) will improve glucose control and insulin sensitivity in diabetic patients with Obstructive Sleep Apnea (OSA).

Hypothesis: Studies have shown sympathetic activation with hypoxic episodes in sleep apnea. In addition, sleep loss has been shown to alter glucose tolerance and possibly increases insulin resistance. Will CPAP prevent hypoxic episodes thereby stopping the sympathetic activation during sleep and improve resistance and tolerance?

Study Design/Methods: Exhaustive search of available medical literature using the following search engines; Medline, Pub Med, EBMRM, CINAHL and MDconsult. The study must have been published in English and contain the following search terms; Type 2 diabetes, obstructive sleep apnea and CPAP. Due to the rapid release if research data in this area, the search was also limited to studies published in the last six years.

Results: Obstructive Sleep Apnea and type 2 diabetes have long shared one common denominator, obesity. The five studies included in this systematic review attempted to limit discussion to factors that may suggest a causal relationship between these two disorders. There was only one study that offered a randomized, double-blinded, placebo controlled study by using a sham CPAP machine and was able to weigh the results independently against a control group and subsequently raise important questions regarding the other studies. The four other studies all reported significant positive results in glycemic and insulin control when implementing CPAP. They were single arm, single center non randomized prospective studies.

Conclusion: Many cardiovascular, metabolic, endocrinological, and neurovascular variables exist that would slow or inhibit a prompt response to a therapy. Other authors noted conflicting results could be attributed to differences in sample sizes, duration of study, lack of objective adherence to data and possible changes in body composition. Only one study suggest there is no causal or therapeutic relationship between these two disorders and therefore treating OSA with CPAP will not independently affect diabetic outcomes. Previous research presented strong conclusions suggesting such a relationship however were weak in study design. Intuitively it seems that activation of the sympathetic nervous system and sleep loss would affect diabetic control however this was not reliably proven in these studies. Given the equivocal results it would be too early for the clinician to modify treatment in reliance on research to date although this area of study has some promise and further research might reveal some more definitive answers in the future.

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The Effects of Continuous Positive Airway Pressure in Type 2 Diabetic Patients with Newly Diagnosed Obstructive Sleep Apnea

Sean Brown

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 15, 2009

Faculty Advisor: Mary Von
Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC
Biography

Sean Brown is a “native” of South Dakota, California, New Mexico, Colorado, Idaho and Oregon. He received his undergraduate degree in one of the nation’s first Bachelor of Science paramedic programs at the University of New Mexico in 2000 and has worked as a Paramedic and professional firefighter. Most recently he was a firefighter/Paramedic and EMS training coordinator for Kootenai County Fire and Rescue in Post Falls Idaho. He is married to Penelope Brown and is the father of three children; Madelynn, Michaela and Mason.
Abstract

**Background:** Type 2 diabetes is a major epidemic in the United States, with an estimated 23.6 million diabetics or 7.8% of the population according to the National Diabetic Information Clearinghouse. Obstructive Sleep Apnea is also a major epidemic affecting 4-17% of the population. Each of these disorders, independently, can lead to increased morbidity and mortality. Rapidly developing research suggests these disorders share many important factors that must be investigated further.

**Purpose of Study:** To determine if continuous positive airway pressure (CPAP) will improve glucose control and insulin sensitivity in diabetic patients with Obstructive Sleep Apnea (OSA). **Hypothesis:** Studies have shown sympathetic activation with hypoxic episodes in sleep apnea. In addition, sleep loss has been shown to alter glucose tolerance and possibly increases insulin resistance. Will CPAP prevent hypoxic episodes thereby stopping the sympathetic activation during sleep and improve resistance and tolerance?

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**Conclusion:** Many cardiovascular, metabolic, endocrinological, and neurovascular variables exist that would slow or inhibit a prompt response to a therapy. Other authors noted conflicting results could be attributed to differences in sample sizes, duration of study, lack of objective adherence to data and possible changes in body composition. Only one study suggest there is no causal or therapeutic relationship between these two disorders and therefore treating OSA with CPAP will not independently affect diabetic outcomes. Previous research presented strong conclusions suggesting such a relationship however were weak in study design. Intuitively it seems that activation of the sympathetic nervous system and sleep loss would affect diabetic control however this was not reliably proven in these studies. Given the equivocal results it would be too early for the clinician to modify treatment in reliance on research to date although this area of study has some promise and further research might reveal some more definitive answers in the future.
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List of Abbreviations

OSA……………………………………………………………………...……..Obstructive Sleep apnea
CPAP...............................................................................................Continuous Positive Airway Pressure
AHI……………………………………………………………………………..Apnea Hypoapnea Index
CGMS……………………………………………….................Continuous Glucose Monitoring System
ESS……………………………………………………………………………Epworth Sleepiness Score
HOMA…………………………………………………………………Homeostatic Model Assessment
HbA1c……………………………………………………………………...Glycosylated Hemoglobin
ISI………………………………………………………………………………Insulin Sensitivity Index
BMI……………………………………………………………………………………Body Mass Index
SDB………………………………………………………………………….Sleep Disordered Breathing
The Effects of Continuous Positive Airway Pressure in Type 2 Diabetic Patients with Newly Diagnosed Obstructive Sleep Apnea

Introduction

According to the National Diabetic Information Clearinghouse, type 2 diabetes is a major epidemic in the United States with an estimated 23.6 million diabetics or 7.8% of the population. The National Sleep Foundation credits Obstructive Sleep Apnea (OSA) with epidemic status affecting over 18 million Americans. In addition an estimated 93% of women and 82% of men with obstructive sleep apnea have not been diagnosed. Interestingly, a reported 46% of commercial truck drivers and 14% of professional football players suffer from obstructive sleep apnea. Each of these disorders, independently, can lead to increased morbidity and mortality, however rapidly developing research suggests these disorders share many important factors that must be investigated further.

"Sleep apnea is a general term encompassing two distinct entities", central sleep apnea and obstructive sleep apnea (OSA). Central sleep apnea is a rare disorder where there is abnormal neurological control of the diaphragm during sleep which causes decreased respiratory effort. Obstructive apnea is defined as the total cessation of airflow for 10 seconds or more despite continued ventilator effort. These episodes are associated with a decrease in oxygen saturation of 4% or more. Patients suffering five or more such apneas per hour are considered to have OSA and may see a decrease in oxygen saturation of 30% to 50% in cessation of airflow for 10 seconds or longer.

Maximum prevalence of OSA occurs between the fifth and seventh decade of life. OSA "affects more than 10% of the population over 65 years of age and more men than woman." Young men are two times more likely than women of the same age to develop sleep apnea however, as women go through menopause the numbers converge. Young et al reported the risk for
apnea/hypoapnea events (AHI) more than doubles after menopause. Pashayan and colleagues reported a randomized placebo controlled study in which elderly men received intramuscular testosterone. The participants noted shortened sleep and increased sleep apnea. Studies in women revealed worsening sleep apnea after menopause which resolved with hormone replacement.

The association between OSA and diabetes cannot be ignored. In a report by West et al. the prevalence of OSA in diabetic men was estimated at 23%. Data from both epidemiologic and clinical studies suggest OSA is an independent risk factor for type 2 diabetes and some authors even suggest a “reverse directions of causality”, meaning diabetes may be causing breathing abnormalities during sleep. Furthermore, OSA is believed to lead to chronic stress caused by recurrent hypoxia and cerebral arousals. “These adverse physiologic effects may trigger downstream mechanisms that promote insulin resistance or glucose tolerance.”

Sleep fragmentation and loss, dysregulation of the hypothalamic-pituitary axis, endothelial dysfunction, elevated sympathetic nervous system activity and increase in cytokine and adipokine release primarily from adipose tissue, have all been implicated as potential mechanisms for insulin resistance and glucose tolerance in OSA patients.

Sleep fragmentation and loss leads to impaired glucose tolerance which prolongs glucose clearance, a major factor in the development of type 2 diabetes. Surveys from the National Sleep Foundation have documented self reported sleep duration of Americans has decreased by 1.5-2 hours over the past 40 years. Young adults who reported they sleep less than 7 hours per night, “increased from 16% in 1960 to 37% in 2002”. In addition, another study found that “after 2 days of sleep curtailment lead to higher glucose levels, lower insulin levels, and a 30% increase in appetite for high
caloric density carbohydrates”. Furthermore Ghrelin, a stomach-derived peptide that stimulates
appetite, increased by 28%.\textsuperscript{5}

Elevated sympathetic nervous system activity leads to an increase in gluconeogenesis, lypolysis, muscle glucogen breakdown and oxidative stress which are collectively factors for the onset
of diabetes.\textsuperscript{4,5} In addition, repeated activation of the sympathetic system and subsequent release of epinephrine and norepinephrine can change the vagal response to deoxygination leading to worsening pre-existing coronary artery disease. Activating the sympathetic nervous system in someone with coronary vascular disease can lead to increased cardiac afterload, myocardial work and oxygen demand.\textsuperscript{2}

Many studies have found elevated tumor necrosis factor-alpha and interleukin-6 which are powerful cytokines in OSA that oppose the function of insulin.\textsuperscript{5} Adipose tissue, and particularly abdominal fat, is a “rich source of adipokines and cytokines” that influence insulin sensitivity. Obstructive sleep apnea “may modulate the expression and secretion of the inflammatory mediators from fat and other tissue.” A review of MRI scans found a correlation between OSA and subcutaneous and intra-abdominal fat.\textsuperscript{5} This study reported no correlation with subcutaneous fat in the neck or parapharyngeal region.\textsuperscript{3}

The purpose of this study is to determine if CPAP will improve glucose control and insulin sensitivity in diabetic patients with obstructive sleep apnea. Previous studies have shown sympathetic activation with hypoxic episodes in sleep apnea. Moreover, sleep loss has been shown to alter glucose tolerance and increase insulin resistance. The hypothesis is that CPAP will prevent hypoxic episodes significantly decreasing sympathetic activity during sleep and thereby improving resistance and
tolerance. Proper diagnosis and treatment of OSA in diabetic patients may improve glucose control and subsequently reduce morbidity and mortality for millions of Americans.

In spite of ongoing research into this specific area of study, some of the terms used in the field are less than familiar to those not considered to be specialists. Accordingly a brief but specific introduction to some of these terms is included to facilitate understanding.

Adiponectin- Most common protein secreted by adipocytes. Adiponectin is decreased in obesity and insulin resistance and there is a close association between hypoadiponectinemia, insulin resistance and hyperinsulinemia. Adiponectin expression increases with improved insulin sensitivity and weight loss.7

Actigraphy- Objective exam to determine daytime sleepiness. A small wrist mounted device records activity throughout the day over a one to three week period. The activity is then compared to the wake/sleep pattern data from a polysomnograph.8

Epworth Sleepiness Score (ESS)- used to subjectively screen patients to identify excessive daytime sleepiness by completing a questionnaire. Points range between 0-24 and a score higher than 11 suggests a high probability of a sleep problem.8 (See Table 3)

Polysomnography- determines states of sleep by recording EMG, EEG and REM. If apneic episodes are detected, then airflow, chest movement, SaO2 and CO2 monitors are used.8 In adult OSA, a patient must demonstrate at least five obstructive apneas per one hour of sleep (Apnea, hypoapnea Index or AHI), each lasting at least 10 seconds and associated with at least one of the following; frequent arousals from sleep, bradytachycardia or oxygen desaturation.3
Apnea, Hypoapnea Index (AHI)- measures the frequency and duration of apneas per hour during a polysomnogram.

Continuous Glucose Monitoring System (CGMS)- records data from a subcutaneous sensor every 5 minutes for 72 hours. This provides a continuous profile of glucose levels in the tissue which lag about 13 minutes behind serum glucose levels.\(^3\)

Euglycaemic Hyperinsulinaemic Clamp- A type of CGMS. Babu et al\(^9\) reported when correlated with serum glucose has an accuracy of 96.2\%.\(^9\)

Homeostatic Model Assessment (HOMA)- computer and mathematical method to quantify insulin resistance.\(^10\) General equation \((\text{glucose mg/dL} \times \text{insulin mU/mL})/405.\)

Glycosylated Hemoglobin (Hemoglobin A1c, HbA1c)- Red blood cells are exposed to glucose and become glycosylated without the help of an enzyme, at a rate that is directly proportional to the glucose concentration during the life span of the RBC. Measurements can estimate the average plasma glucose during the last 120 days.\(^11\)

**Methods**

An exhaustive literature search using Medline, Pub Med, EBMRM, MDconsult and CINAHL was conducted using diabetes, sleep apnea and CPAP as search terms. Articles were limited to the English language and to those published in the last 6 years. This is a relatively short time frame however there is a significant amount of research in this area with many new studies annually. Only articles that look at the effects of CPAP on type 2 diabetes were included. (Table 1)
Results

Five studies were included in this review. One randomized controlled, double-blinded trial and four single center, single arm, non-randomized trials. (See Table 2)

Harsch et al\textsuperscript{12} attempted to determine if OSA is an independent risk factor for increased insulin resistance in diabetics. Nine diabetics were selected, placed on CPAP, and insulin sensitivity index (ISI) was measured at 2 days and at 3 months. The patients included 7 males and 2 postmenopausal females with type 2 diabetes and OSA with a mean age of 56.3 years. They noted the mean HbA1c of their population was 6.4\% which is significantly lower than most of the previous studies. Patients with severe co-morbid conditions such as; malignancies, liver disease and other endocrine disorders were excluded. In addition, TSH and insulin like growth factor-I had to be within normal limits. Patients with hyperlipidemia and hypertension as well as those treated with calcium channel blockers and ACE inhibitors were included. Patients treated with beta-blockers or steroids were excluded.\textsuperscript{12}

Insulin responsiveness was measured by a hyperinsulinaemic euglycaemic clamp which is considered the gold standard in sensitivity measurement.\textsuperscript{12} CPAP compliance was documented by built in data stores and was downloaded after every 47 days of use. In addition, patients underwent an investigation for peripheral and autonomic diabetic neuropathy due to its documented relationship with sleep disordered breathing.\textsuperscript{12}

The results found ISI was unchanged after two days but significantly improved after 3 months (47\%). Hemaglobin A1c however was not affected. Harsch et al\textsuperscript{12} reported these results varied from their earlier study in which they looked at ISI after the same treatment in 40 \textit{non diabetics} with OSA. In the non diabetic group there was rapid and significant improvement in insulin sensitivity even after
2 days of therapy. They noted there was no significant difference in age or BMI between the 9 diabetic patients and the 40 non-diabetic patients. Harsch et al\textsuperscript{12} attributed these different findings to the “fixed and genetically determined degree of insulin resistance, which is thus more difficult to reverse in diabetic than non-diabetic patients”.

They also speculated that 4 of 9 of the diabetic patients were on Metformin therapy which had made them more responsive to improving insulin sensitivity. This is the only study to provide data on which anti-diabetic medications patients were taking. In their diabetic study they reported good CPAP compliance with a mean usage of 5.8 hrs/night. In addition, one patient lost 21kg during the study and no longer required medication, otherwise there was no significant change in BMI.

Babu et al\textsuperscript{9} produced the most substantial positive findings with their study assessing the effects of CPAP treatment in SDB on glycemic control in a group of obese patients with type 2 diabetes. Their subjects were diabetic patients who met the clinical criteria for OSA. This study focused on patients with hemoglobin A1c greater than 7% but did not exclude those with a lower HbA1c. Forty-two were enrolled after meeting the inclusion criteria and 25 were available for final analysis with all “lost” patients accounted for.\textsuperscript{9}

The patients had a mean age of 50.7 years, 16 were men, a mean baseline HbA1c was 8.3% and the mean BMI was 42.7. Twenty-four of the twenty-five patients used machines that allowed for adherence monitoring. The group underwent baseline glucose, HbA1c and 72-hour continuous glucose monitoring with ongoing maintenance of a food diary before CPAP initiation which was unique to this study. The subjects were scheduled to return between 30-90 days for repeat polysomnography and 72 hour/food diary testing. Compliance of CPAP was considered four hours or more per night.\textsuperscript{9}
The results were significant. Mean CPAP treatment was 83 days. Mean 1 hour postprandial glucose values were significantly reduced for breakfast (191 mg/dL to 130 mg/dL) lunch (196 mg/dL to 138 mg/dL) and dinner (199 mg/dL to 137 mg/dL). In 17 patients with HbA1c greater than 7%, HbA1c was reduced by a mean 9.2% to 8.6%. Further analysis of this sub group revealed a significant decrease in total number of serum glucose readings of 200 mg/dL or greater with a mean reduction from 148 to 83 after CPAP. There was no statistically significant reduction in the 8 with HbA1c less than 7%. This was the only study that found a reduction in HbA1c of statistical significance.9

West et al10 posted the first randomized double blinded trial and also the only to report findings not in support of the proposition that CPAP improves glucose control and insulin sensitivity. Patients were type 2 male diabetics, referred to a sleep clinic between June 2004 and August 2005, who had not yet initiated CPAP therapy for their newly diagnosed OSA. Patients were excluded if they required “urgent CPAP or had unstable diabetes”. Forty-two patients were enrolled after meeting inclusion criteria.10

Patients were randomized into a CPAP group and a placebo group. The placebo group utilized the same machines which were set to the lowest setting with a flow restrictor and additional holes in the mask to prevent rebreathing. Insulin resistance was measured using both the HOMA and hyperinsulinaemic euglycaemic clamp. HbA1c, lipids, adiponectin, CRP, height, weight and BMI were recorded as well as neck, waist and hip measurements. Body composition was measured using bioelectrical impedance analysis to determine if fat distribution was affected. Subjective sleepiness was measured by the Epworth Sleepiness Score (ESS). Objective sleepiness was measured by the Maintenance of Wakefulness test (MWT). Duration of the study was 3 months.10
Twenty-one men were randomized to the CPAP group and 21 were randomized to the placebo group. One patient from the CPAP group was found to have a defective machine that delivered minimal pressure so his data was transferred to the placebo group. There were no significant differences between the groups in age, diabetic treatment and severity of OSA. One patient was lost from the treatment group due to hospital admission for emergency cardiac surgery and 9 patients did not receive the second Euglycaemic clamp due to “technical difficulties”.¹⁰

As expected, there was significant change in measures of daytime sleepiness with the therapeutic group. There was a slight positive change in insulin sensitivity expressed as the quantity of glucose metabolized (M) per unit in plasma insulin concentration (I) with data from the Euglycaemic clamp. M/I had increased 1.7 in the therapeutic CPAP group compared to a decrease of 5.7 in the placebo group. A positive change indicates improved sensitivity. There was, however, no statistically significant change in the HOMA, Adiponectin, weight, BMI, waist to hip ratio, lipids or CRP. Mean hours of CPAP use in the therapeutic group was 3.3 hours and 3.5 hours in the placebo group.¹⁰

Dawson et al¹³ developed a study to focus on the short term effects of CPAP on glucose during sleep in diabetic patients with newly diagnosed OSA. The interstitial glucose level was monitored during a polysomnogram and patients with an AHI greater than 15 were allowed to continue the study. CPAP was initiated for at least 3 more weeks with a mean use of 41 days, and then both the polysomnogram and interstitial glucose monitoring were repeated. The primary end point was to determine the mean interstitial glucose for all 30 second recordings, during a complete polysomnogram, in addition to the calculating the mean 24 hour interstitial glucose and postprandial level after breakfast.¹³
The participants were required to use the CPAP a minimum of 4 hours a night and 3 ultimately were excluded from the study for non compliance. Twenty eight subjects completed the first night of the study and 22 completed the second night with all the “lost” accounted for. In addition, one participant was dropped after showing many central apneas and another because she was the only type 1 diabetic in the study.13

Eighteen had a BMI greater than 30 and ten were greater than 40. Sixteen had severe sleep apnea and 8 diabetics had an HbA1c greater than 7%. Twelve subjects gained weight between the studies with 6 gaining more than 2kg. The mean sleeping glucose decreased from 122 mg/dL to 102.9 mg/dL and the median standard deviation in glucose variance decreased from 20.0 mg/dL to 13.0 mg/dL. There were no significant changes in the mean daytime glucose from 0700 hours and 2300 hours and HbA1c. It was noted that while the mean number of days on CPAP was 41, there were only 3 subjects who had 60 or more days of CPAP use.13

Pallayova et al6 developed a very similar study, in which diabetics with newly diagnosed OSA, underwent several days of continuous interstitial glucose monitoring and then returned to a sleep clinic for CPAP titration and glucose monitoring. Fourteen participants completed the study and the results were very similar to those in Dawson. There were 25,304 continuous glucose measurements obtained, with 473 paired capillary glucose measurements for confirmation, and a total average of 150.5 hours of glucose monitoring per patient. The results revealed a statistically significant decrease in mean nocturnal glycemia and glucose variability.6

Discussion
Obstructive Sleep Apnea and type 2 diabetes have long shared one common denominator, obesity. The five studies included in this systematic review attempted to limit additional factors that
may suggest a causal relationship between these two disorders. Unfortunately, there was only one well
designed trial that offered a randomized, double-blinded, placebo controlled study. West et al\textsuperscript{10} was
the only group to use a sham CPAP machine and were able to weight the results independently against
a control group and subsequently raise important questions regarding the other studies. What are the
behavioral influences on study results?

All studies used a continuous glucose monitoring system which is required to determine
glucose variability, and both Harsch et al\textsuperscript{12} and West et al\textsuperscript{10} specifically identified the use of a
Hyperinsulinaemic Euglycaemic Clamp. All studies except Pallayova took measures to ensure CPAP
compliance which is a major issue with newly diagnosed OSA patients.\textsuperscript{6, 9, 10, 12, 13} Harsch et al\textsuperscript{14},
Babu et al\textsuperscript{9} and West et al\textsuperscript{10} all used machines that recorded usage data. Dawson and colleagues used
weekly follow-ups to ensure compliance but was also the most aggressive, excluding 3 participants
who did not meet their 4 hour usage criterion.\textsuperscript{13}

West et al\textsuperscript{10} included the lowest compliance numbers with mean hours of use at 3.3 in the
therapeutic group and 3.6 hours in the placebo group. They argue low compliance was not a significant
factor since these hours also produced significant improvement in OSA and therefore should have
decreased nocturnal sympathetic activity and glucose variations. Accordingly, they did not follow the
example of Dawson in excluding participants not in compliance.\textsuperscript{10}

Study duration varied significantly both between studies and within them. Babu’s patients
varied CPAP usage ± 50 days from the mean of 83 days.\textsuperscript{9} Dawson et al\textsuperscript{13} had a range of 26 to 96 days
and the range in the Pallayova et al\textsuperscript{6} study was unclear.
Harsch et al\textsuperscript{14}, Babu et al\textsuperscript{9}, Dawson et al\textsuperscript{13} and Pallayova et al\textsuperscript{6} were all single-center, single-arm, non-randomized, prospective studies with very similar inclusion and exclusion criteria and endpoints. The number of participants in the studies ranged from 9 in Harsch to 40 in West’s double armed study.\textsuperscript{14} BMI ranged from 36.6 in West et al to 42.7 in Babu et al.\textsuperscript{9,10}

No single study took significant steps to control or monitor diet. Babu and his group perhaps put forth the best effort by asking their participants to complete a food diary when on the 72-hour continuous glucose monitoring. They then were able to confirm the patients’ diet with glucose fluctuations in the glucose test data. In addition they were the only group to look at postprandial results for all meals (0700-2200).\textsuperscript{9}

West et al\textsuperscript{10} did not monitor diet but were the only study to monitor for changes in abdominal adiposity by measuring body composition. West and colleagues raised a very important concerns regarding their findings by questioning other studies positive results without improved, and in some cases, increased BMI. When considering the effects of abdominal adiposity on glucose metabolism, they stated the results may have shown improvement due to “changes in body fat distribution” and not due to CPAP use.\textsuperscript{10} Moreover, it was noted that these changes would not have been reflected in a simple BMI measurement.

This study also raises a very important argument when looking at continuous glucose monitoring. Not only is it more likely people would to modify their behavior either by medication compliance, food choices or CPAP compliance when they know they are being monitored, but the testing materials may also alter the results of the studies. West et al\textsuperscript{10} noted hyerinsulinaemic euglycaemic clamp is an intense invasive procedure in which a probe in placed in the abdominal tissue. This procedure in and of itself would cause a significant amount of anxiety and increase sympathetic
activity. Over time, with repeat procedures, that anxiety would diminish. West et al points out that, in studies without a control, a researcher may interpret these results as a positive finding for the intervention or therapy, as opposed to an incidental reaction to a specific event. It is not clear if this occurred in the other studies including the Harsch et al study referred to by West et al.

West et al noted, when treatment and placebo are compared, there was not a significant improvement in glucose tolerance when looking at the euglycemic clamp. Babu et al argued they compared their population with and without CPAP so they were controlled against themselves. Of course this design is not randomized, blinded or placebo controlled.

HbA1C ranged from 6.4 in Harsch et al to 8.5 in West et al’s therapeutic group with Babu et al as the only study showing HbA1c improvement of statistical significance. Harsch et al was the only study to significantly outline the current diabetic treatment for each participant and whether he or she was currently being treated with an insulin sensitizing medication such as metformin or thizolididones. When looking at this data however, the metformin patients did not improve significantly more than the others. All of the studies used “stability of diabetic management” as an inclusion criteria, excluding patients recently put on new medications nor did they allow medication changes during the study period.

Conclusion

The studies collected for this review share three common factors, obstructive sleep apnea, type 2 diabetes and obesity. When combining these three disorders and attempting to interpret the data a clinician must remain skeptical. Many cardiovascular, metabolic, endocrinolocial, and neurovascular variables exist that would slow or inhibit a prompt response to a therapy. Tarsal et al noted conflicting results could be attributed to differences in sample sizes, duration of study, lack of objective adherence
to data and possible changes in body composition.\textsuperscript{4} West et al\textsuperscript{10} suggest there is no causal or therapeutic relationship between these disorders and that treating OSA with CPAP will not independently affect diabetic outcomes.\textsuperscript{10} The other studies presented strong conclusions suggesting the existence of such a relationship, however their efforts were weak in study design.

Intuitively it seems activation of the sympathetic nervous system and sleep loss would affect diabetic control however this was not reliably proven in these studies. Given the equivocal results it would be too early for the clinician to modify treatment in reliance on research to date although this area of study has some promise and further research might reveal more definitive answers in the future.
References


Table 1 Summary of Clinical Trials Reviewed

<table>
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<td>n=9</td>
<td>3 months</td>
<td>ISI at baseline, after 2 days, and after 3 months, BMI, HbA1c, Serum Leptin, Polysomnogram, ESS</td>
<td>Significant improvement in insulin sensitivity after 3 months of CPAP use</td>
<td></td>
</tr>
<tr>
<td>Babu et al</td>
<td>Single Centre, Single arm, non-randomized, prospective study</td>
<td>Changes in interstitial glucose levels</td>
<td>n=25</td>
<td>30 to 90 days of treatment</td>
<td>72-hour continuous glucose monitoring, Food Diary, A1c, polysomnography</td>
<td>Significant reduction in HbA1c</td>
<td>No other study has been able to reproduce such dramatic results</td>
</tr>
<tr>
<td>West et al</td>
<td>Randomized, Double-blind Placebo-controlled</td>
<td>Effects of CPAP on insulin resistance</td>
<td>n=40</td>
<td>3 months</td>
<td>ESS, polysomnography, CGMS, HOMA, Body Composition, MWT, HbA1c, Lipids, CRP, Adiponectin</td>
<td>No change in HbA1c, CGMS, Cody Composition, Lipids, CRP, Adiponectin</td>
<td>Only study to use a placebo group, Only study not to find positive results. 7 patients data was lost, unclear from which group.</td>
</tr>
<tr>
<td>Dawson et al</td>
<td>Single Centre, Single arm, non-randomized, prospective study</td>
<td>Measure interstitial glucose during two polysomnograms at baseline and after a mean of 41 days</td>
<td>n=20</td>
<td>26 to 96 days</td>
<td>Polysomnogram, HbA1c, CGMS</td>
<td>Mean sleeping glucose and glucose variability decreased significantly</td>
<td>No control group, Large variance in duration of CPAP before retesting, Many variables such as diet and medication.</td>
</tr>
<tr>
<td>Pallayova et al</td>
<td>Single Centre, Single arm, non-randomized, prospective study</td>
<td>Will CPAP prevent apnea-related glucose fluctuations</td>
<td>n=14</td>
<td>unknown</td>
<td>CGMS, Polysomnography</td>
<td>Significant reduction in glucose variability with the initiation of CPAP</td>
<td>No control group</td>
</tr>
</tbody>
</table>
Table 2  Results of Clinical Trials Reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harsch et al 2004</td>
<td>- Insulin sensitivity was unchanged after 2 days of CPAP but significantly improved after 3 months</td>
</tr>
<tr>
<td></td>
<td>- HbA1c and BMI were unaffected</td>
</tr>
<tr>
<td></td>
<td>- No correlation with Leptin levels</td>
</tr>
<tr>
<td>Babu et al 2005</td>
<td>- Significant reduction of 1-hour postprandial glucose levels after 83 ± 50 days of CPAP use</td>
</tr>
<tr>
<td></td>
<td>- Significant reduction in HbA1c in patients with starting A1c &gt; 7% after CPAP use</td>
</tr>
<tr>
<td>West et al 2007</td>
<td>- No significant change in glycaemic control and insulin resistance in either therapeutic or placebo groups</td>
</tr>
<tr>
<td></td>
<td>- BMI and body habitus were unchanged</td>
</tr>
<tr>
<td></td>
<td>- No correlation between CPAP use and diabetic control</td>
</tr>
<tr>
<td></td>
<td>- Improved Epworth Sleepiness Score in therapeutic group</td>
</tr>
<tr>
<td>Dawson et al 2008</td>
<td>- Mean sleeping glucose and glucose variability levels decreased after CPAP use</td>
</tr>
<tr>
<td></td>
<td>- No significant change in HbA1c</td>
</tr>
<tr>
<td>Pallayova et al 2008</td>
<td>- Significant reduction in glucose variability with the use of CPAP</td>
</tr>
<tr>
<td></td>
<td>- No significant change in HbA1c</td>
</tr>
</tbody>
</table>
Table 3

**Epworth Sleepiness Scale**

How Likely are you to doze off or fall asleep in the following situations?
Answer considering how you have felt over the past one to two weeks

0 = Would never doze  
1 = Slight chance of dozing  
2 = Moderate chance of dozing  
3 = High chance of dozing

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sitting and reading</td>
</tr>
<tr>
<td>2</td>
<td>Watching TV</td>
</tr>
<tr>
<td>3</td>
<td>Sitting inactive in a public place</td>
</tr>
<tr>
<td>4</td>
<td>As a passenger in a car for an hour without breaks</td>
</tr>
<tr>
<td>5</td>
<td>Lying down to rest in the afternoon when able</td>
</tr>
<tr>
<td>6</td>
<td>Sitting and talking to someone</td>
</tr>
<tr>
<td>7</td>
<td>Sitting quietly after a lunch without alcohol</td>
</tr>
<tr>
<td>8</td>
<td>In a car while stopped for a few minutes in traffic</td>
</tr>
</tbody>
</table>

Total= __________