Effect of continuous positive airway pressure therapy on glucose control

Salim Surani, Shyam Subramanian

Surani S, Subramanian S. Effect of continuous positive airway pressure therapy on glucose control. World J Diabetes 2012; 3(4): 65-70 Available from: URL: http://www.wjgnet.com/1948-9358/full/v3/i4/65.htm DOI: http://dx.doi.org/10.4239/wjd.v3.i4.65

INTRODUCTION
Obstructive sleep apnea (OSA) is characterized by episodic and repetitive upper airway narrowing during sleep that leads to a well recognized clinical syndrome of snoring and excessive daytime sleepiness[1]. OSA has been independently associated with hypertension and cardiovascular disease[2]. A high prevalence rate is being increasingly recognized, particularly in patients with metabolic syndrome, and several studies have suggested an independent association between OSA and insulin resistance (IR) and glycemic control[3-11].

EPIDEMIOLOGY
A recent study from France followed 806 elderly subjects over 7 years and found an independent association between sleep apnea and metabolic syndrome, even after correcting for age, gender and obesity[12]. A prospective study from Japan that spanned five years, examined nocturnal oximetry in over 4000 patients and calculated that a multivariable-adjusted hazard ratio (95% CI) for developing type 2 diabetes was 1.69 (1.04-2.76) among those with moderate to severe nocturnal intermittent hypoxia[12]. A Veterans Affairs based observational cohort study examined 1233 consecutive patients referred for evaluation of OSA, of whom 544 were free from pre-existing diabetes. At a median follow-up time of 2.7 years, they found a multivariable-adjusted hazard ratio of 1.43 per quartile for incident diabetes[13]. In a case control study from Ja-
**Table 1 Effect of continuous positive airway pressure on blood glucose control**

| Study                        | Study design/cohort | Sample size | Control group | Outcome/measurements | Study duration | Conclusions |
|------------------------------|---------------------|-------------|---------------|----------------------|----------------|-------------|
| Stohr et al[36]              | OSA patients        | 5           | None          | Fasting glucose and insulin | 2 mo           | No change in either fasting or nocturnal insulin level |
| Saini et al[37]              | OSA patients BMI 32.7 ± 2.3 Kg/m² | 8 | None          | Glucose and insulin every 10 min interval during sleep | 1 night         | Mean insulin and glucose did not differ between pre treatment and treatment night |
| Davies et al[38]             | OSA patients        | 10          | Matched control | Fasting insulin, lipid profile | 3 mo           | No change in insulin level with CPAP |
| Brooks et al[39]             | OSA patients with BMI 42.7 ± 4.3 Kg/m² | 10 | None          | Hyperinsulinemic euglycemic clamp | 4 mo           | Improvement in insulin responsiveness seen |
| Cooper et al[40]             | OSA patients        | 6           | None          | Insulin and c-peptide sample every hour and glucose sample every 30 min during sleep | 1 night         | No changes in glucose, insulin and C-peptide with CPAP treatment |
| Saarelainen et al[41]        | OSA patients        | 7           | None          | Hyperinsulinemic euglycemic clamp | 3 mo           | No change in insulin responsiveness |
| Pierzchala et al[42]         | Type 1 and type 2 diabetes patients with OSA | 30 | None          | Blood glucose | 6 mo           | Better blood glucose control |
| Chin et al[43]               | OSA patients        | 22          | OSA patients | Oral glucose tolerance test with insulin measurement | 6 mo           | No change in glucose and insulin level except in patients who have lost weight |
| Ip et al[44]                 | OSA patients        | 30          | Matched 30 non-OSA control | Fasting glucose and insulin | 6 mo           | No change in fasting glucose and insulin seen (decrease in Leptin and triglyceride was seen) |
| Smurra et al[45]             | 16 OSA patients; 10 from endocrine clinic and 6 other OSA patients | 16 | None          | Oral glucose tolerance test in 10 patients and hyperinsulinemic euglycemic clamp in 6 patients | 2 mo           | No change in mean glycemia, insulin level or insulin responsiveness was seen |
| Harsch et al[46]             | OSA patients        | 40          | None          | Hyperinsulinemic euglycemic clamp | 3 mo           | Improvement in insulin sensitivity at day 2 and 3 mo, in patient with BMI < 30, than in patients with BMI > 30 |
| Harsch et al[47]             | Type 2 diabetes patients with OSA | 9           | None          | Hyperinsulinemic euglycemic clamp | 3 mo           | Insulin sensitivity was unchanged after 2 days, but significantly improved after 3 mo; glycemic control was unaffected after 3 mo |
| Babu et al[48]               | Type 2 diabetes patients with OSA | 25          | None          | HBA1c and post prandial blood glucose | 3 mo           | Decrease in HBA1c and postprandial am glucose level |
| Czupryniak et al[49]         | Non diabetic OSA patients | 9           | None          | Continuous glucose monitoring, plasma insulin, HOMA-IR | 1 night         | Mean blood glucose, fasting insulin and HOMA-IR were significantly higher with CPAP treatment |
| Hassaballa et al[50]         | Type 2 diabetes and OSA (retrospective) | 38          | None          | HBA1c | Approx. 3 mo | Decrease in HBA1c was seen with CPAP therapy |
| Lindberg et al[51]           | OSA patients        | 28          | Matched control without OSA | HOMA and fasting insulin | 6 mo           | Decrease in insulin resistance and fasting insulin |
| West et al[52]               | Type 2 diabetes and OSA | 42          | Randomized, double blind | HOMA, hyperinsulinicaemic euglycemic clamp, HBA1c, highly sensitive C-reactive protein | 3 mo           | No change in glycemic control or insulin resistance |
| Coughlin et al[53]           | OSA patients        | 34          | Randomized placebo-controlled blinded crossover trial | Insulin, fasting glucose, HOMA-IR | 6 wk           | No change in glucose or insulin resistance |
| Pallayova et al[54]          | Type 2 diabetes with OSA | 14          | None          | Continuous glucose monitoring HOMA | Several d       | Reduction in nocturnal glucose variability and improved overnight glucose control |
| Wang et al[55]               | Type 2 diabetes and OSA | 30          | None          | Continuous glucose monitoring HOMA | 7 d           | Improve ISI |
pan, Kono et al. found that OSA severity as assayed by apnea-hypopnea index (AHI) was a strong predictor of a number of metabolic syndrome parameters, such as hypertension, hyperglycemia and dyslipidemia, while body mass index and lowest arterial oxygen saturation during sleep did not. A British study involving patients with type 2 diabetes and the use of structured questionnaires and overnight oximetry found a 23% prevalence of OSA. The Wisconsin sleep study found an increased incidence of diabetes in patients with OSAS, but the significance of OSAS disappeared after accounting for obesity. In examining results from the Sleep Heart Health study involving 2656 subjects, Punjabi et al. found that there was a relationship between OSA severity as measured by both AHI and degree of sleep-related oxygen desaturations and IR. More recently, the same investigators used an intravenous glucose tolerance test; BMI: Body mass index; OSA: Obstructive sleep apnea; CPAP: Continuous positive airway pressure.

HOMA-IR: Homeostatic model assessment of insulin resistance; HBA1c: Glycosylated Hemoglobin; ISI: Insulin sensitivity index; OGTT: Oral glucose tolerance test; BMI: Body mass index; OSA: Obstructive sleep apnea; CPAP: Continuous positive airway pressure.

### Effects on Adipocytes

In a study involving 270 patients with BMI ≥ 25, Adiponectin is an important adipokine with protective effects against insulin resistance. At least two studies have examined the relationship between adipocytes exposed to in vitro intermittent hypoxia and have shown that adiponectin production, despite a significant upregulation of adiponectin mRNA expression, Sleep disruption is an additional, potentially important mechanism by which OSA may affect metabolism. In healthy subjects, sleep restriction was associated with IR, increased appetite and craving for carbohydrates. Disruption of normal sleep architecture has also been shown to induce a pro-inflammatory state, with increased release of interleukin (IL)-6 and tumor necrosis factor (TNF)-α by circulating monocytes. Sleep apnea has also been postulated to lead to dysregulation of the hypothalamic-pituitary axis and this may well play a central role in modulating insulin resistance and a predisposition to diabetes mellitus. Nocturnal awakenings have been shown to be associated with pulsatile cortisol release and autonomic activation.

### EFFECT OF CPAP THERAPY ON IR

Continuous positive airway pressure (CPAP) has emerged as an effective therapy for OSA. In view of the evidence that OSA can lead to insulin resistance and abnormality in glucose metabolism, studies have been done by several investigators to see if CPAP therapy, in addition to eliminating apnea, hypopnea, desaturation and sympathetic surge in turn, can lead to improvement in insulin resistance and blood glucose control. We will undertake a review of the literature as it pertains to the effect of CPAP in blood sugar control and insulin resistance.
EFFECT OF CPAP ON GLUCOSE METABOLISM

A multitude of studies have explored the influence of CPAP therapy on blood sugar control. Many of these have had issues with study design, including the lack of a control group and small sample size. These studies are summarized in Table 1.

CONCLUSION

There is a strong association between OSA and diabetes mellitus. A multitude of pathophysiological perturbations have been demonstrated both in vitro and in vivo that demonstrate a close interrelationship, including inflammatory mediators of oxidative stress, as well as leptin resistance and hypothalamo-pituitary axis dysregulation. These effects are mediated secondary to both the effect of intermittent hypoxia as well as sleep fragmentation. Treatment with nightly CPAP leads to a resolution of both these behaviors and has been shown to be effective, not only in resolving daytime sleepiness, but also improving cardiovascular mortality. The data on the impact, if any, and its magnitude on glycemic control as well as the impact of complete resolution of OSA with adequate CPAP compliance (adequately powered and randomized controlled design) on the metabolic profile of patients with OSA and diabetes mellitus in both obese and non-obese cohorts.

REFERENCES

1. Stradling JR, Davies RJ. Sleep. 1: Obstructive sleep apnoea/hypopnoea syndrome: definitions, epidemiology, and natural history. Thorax 2004; 59: 73-78
2. Lattimore JD, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol 2003; 41: 1429-1437
3. Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. Eur Heart J 2004; 25: 735-741
4. Tasali E, Mokhlesi B, Van Cauter E. Obstructive sleep apnea and type 2 diabetes: interacting epidemics. Chest 2008; 133: 496-506
5. Levy P, Bonsignore MR, Eckel J. Sleep, sleep-disordered breathing and metabolic consequences. Eur Respir J 2009; 34: 243-260
6. Strohl KP, Novak RD, Singer W, Cahan C, Boehm KD, Donko CW, Hofstrem VS. Insulin levels, blood pressure and sleep apnea. Sleep 1994; 17: 614-618
7. Stoons RA, Facchini F, Guilleminault C. Insulin resistance and sleep-disordered breathing in healthy humans. Am J Respir Crit Care Med 1996; 154: 170-174
8. Resnick HE, Redline S, Shahar E, Gilpin A, Newman A, Walter R, Ewy GA, Howard BV, Punjabi NM. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. Diabetes Care 2003; 26: 702-709
9. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R,
Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol* 2004; 160: 521-530

10 Punjabi NM, Polotsky YV. Disorders of glucose metabolism in sleep apnea. *J Appl Physiol* 2005; 99: 1998-2007

11 Assoumou HG, Gaspoz JM, Sforza E, Pichot V, Celle S, Maudoux D, Kosovssky M, Chouchou F, Barthelemy JC, Roche F. Obstructive sleep apnea and the metabolic syndrome in an elderly healthy population: the SYNAPSE cohort. *Sleep Breath* 2011; Epub ahead of print

12 Muraki I, Tanigawa T, Yamagishi K, Sakurai S, Ohira T, Imano H, Kitamura A, Kiyama M, Sato S, Shimamoto T, Konishi M, Iso H. Nocturnal intermittent hypoxia and the development of type 2 diabetes: the Circulatory Risk in Communities Study (CIRCS). *Diabetologia* 2010; 53: 481-488

13 Botros N, Conato J, Molsenen V, Selim B, Doctor K, Yaggi HK. Obstructive sleep apnea as a risk factor for type 2 diabetes. *Am J Med* 2009; 122: 1122-1127

14 Kono M, Tatsumi K, Saibara T, Nakamura A, Tanabe N, Takiguchi Y, Kuriyama T. Obstructive sleep apnea syndrome is associated with some components of metabolic syndrome. *Chest* 2007; 131: 1387-1392

15 West SD, Nicoll DJ, Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax* 2006; 61: 945-950

16 Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. *Am J Respir Crit Care Med* 2005; 172: 1590-1595

17 Punjabi NM, Beamer BA. Alterations in Glucose Disposal in Sleep-disordered Breathing. *Am J Respir Crit Care Med* 2009; 179: 235-240

18 Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 2002; 165: 670-676

19 Ye J, Gao Z, Yin J, He Q. Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. *Am J Physiol Endocrinol Metab* 2007; 293: E1118-E1128

20 Hosogai N, Fukuhara A, Oshima K, Miyata Y, Tanaka S, Segawa K, Furukawa S, Tochino Y, Komuro R, Matsuda M, Shimomura I. Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes* 2007; 56: 901-911

21 Chen B, Lam KS, Wang Y, Wu D, Lam MC, Shen J, Wong L, Hoo RL, Zhang J, Xu A. Hypoxia dysregulates the production of adiponectin and plasminogen activator inhibitor-1 in independent of reactive oxygen species in adipocytes. *Biochem Biophys Res Commun* 2006; 341: 549-556

22 Magalang UJ, Cruff JP, Rajappan R, Hunter MG, Patel T, Marsh CB, Raman SV, Parinandi NL. Intermittent hypoxia suppresses adiponectin secretion by adipocytes. *Exp Clin Endocrinol Diabetes* 2007; 117: 129-134

23 Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007; 11: 163-178

24 Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004; 141: 846-850

25 Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleepl 2007; 30: 1145-1152

26 Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med* 2006; 166: 1756-1762

27 Buckley TM, Schatzberg AF. On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. *Clin Endocrinol Metab* 2005; 90: 3106-3114

28 Späth-Schwalbe E, Goffeje M, Kern W, Born J, Fehm HL. Sleep disruption alters nocturnal ACTH and cortisol secre- tory patterns. *Biol Psychiatry* 1991; 29: 575-584

29 Strohls FA, Fachhini FS, Philip P, Valencia-Flores M, Guillemault C. Selected cardiovascular risk factors in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure (n-CPAP). *Sleep 1993; 16: S141-S142

30 Saini J, Krieger J, Brandenberger G, Wittersheim G, Simon C, Follenius M. Continuous positive airway pressure treatment. Effects on growth hormone, insulin and glucose profiles in obstructive sleep apnea syndrome. *Horm Metab Res 1993; 25: 375-381

31 Davies RJ, Turner R, Crosby J, Stradling JR. Plasma insulin and lipid levels in untreated obstructive sleep apnoea and snoring; their comparison with matched controls and re- sponse to treatment. *J Sleep Res 1994; 3: 180-185

32 Brooks B, Cistulli PA, Borkman M, Ross G, McGhee S, Grunstein RR, Sullivan CE, Yue DK. Obstructive sleep apnea in obese nonsmoker-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness. *J Clin Endocrinol Metab 1994; 79: 1681-1685

33 Cooper BG, White JE, Ashworth LA, Alberti KG, Gibson GJ. Hormonal and metabolic profiles in subjects with obstructive sleep apnea syndrome and the acute effects of nasal continuous positive airway pressure (CPAP) treatment. *Sleep 1995; 18: 172-179

34 Saarelainen S, Lahtela J, Kallonen E. Effect of nasal CPAP treatment on insulin sensitivity and plasma leptin. *J Sleep Res 1997; 6: 146-147

35 Pierzchała W, Ograbek M. [Sleep apnea syndrome in pa- tients with diabetes. Effectiveness of treatment for respira- tory assistance at night with continuous positive airway pressure]. *Wiad Let* 1998; 51: 166-172

36 Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakamura T, Nakao K, Ohi M. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation 1999; 100: 706-712

37 Ip MS, Lam KS, Ho C, Tsang KW, Lam W. Serum leptin and vascular risk factors in obstructive sleep apnea. *Chest* 2000; 118: 580-586

38 Smurra M, Philip P, Taillard J, Guillemault C, Bioulac B, Gán H. CPAP treatment does not affect glucose-insulin me- tabolism in sleep apneic patients. *Sleep Med 2001; 2: 207-213

39 Harsh IA, Schahin SP, Radespiel-Tröger M, Weintz O, Jahrreiss H, Fuchs FS, Wiest GH, Hahn EG, Lohmann T, Kon- turek PC, Ficker JH. Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2004; 169: 156-162

40 Harsh IA, Schahin SP, Brückner K, Radespiel-Tröger M, Fuchs FS, Hahn EG, Konturek PC, Lohmann T, Ficker JH. The effect of continuous positive airway pressure treatment on insulin sensitivity in patients with obstructive sleep apnoea syndrome and type 2 diabetes. *Respiration 2004; 71: 252-259

41 Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T. Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. *Arch Intern Med 2005; 165: 447-452

42 Czupryniak I, Loba J, Pawlowski M, Nowak D, Bialasiewicz P. Treatment with continuous positive airway pressure may affect blood glucose levels in non diabetic patients with ob- structive sleep apnea syndrome. *Sleep 2005; 28: 601-603

43 Hassaballa HA, Tulaimain T, Herdegen J, Mokhlesi B. The effect of continuous positive airway pressure on glucose con- trol in diabetic patients with severe obstructive sleep apnea.
Lindberg E, Berne C, Elmasry A, Hedner J, Janson C. CPAP treatment of a population-based sample—what are the benefits and the treatment compliance? *Sleep Med* 2006; 7: 553-560

West SD, Nicoll DJ, Wallace TM, Matthews DR, Stradling JR. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. *Thorax* 2007; 62: 969-974

Coughlin SR, Mawdsley L, Mugarza JA, Wilding JP, Calverley PM. Cardiovascular and metabolic effects of CPAP in obese males with OSA. *Eur Respir J* 2007; 29: 720-727

Pallayova M, Donic V, Tomori Z. Beneficial effects of severe sleep apnea therapy on nocturnal glucose control in persons with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2008; 81: e8-11

Wang H, Wang L, Liu J. [The effect of short-time continuous positive airway pressure treatment on insulin sensitivity in patients with obstructive sleep apnea-hypopnea syndrome and type 2 diabetes]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2008; 22: 597-599

Dawson A, Abel SL, Loving RT, Dailey G, Shadan FF, Cronin JW, Kripke DF, Kline LE. CPAP therapy of obstructive sleep apnea in type 2 diabetics improves glycemic control during sleep. *J Clin Sleep Med* 2008; 4: 538-542

Steiropoulos P, Papanas N, Nena E, Tsara V, Fitili C, Tzouvelekis A, Christaki P, Maltezos E, Bournos D. Markers of glycemic control and insulin resistance in non-diabetic patients with Obstructive Sleep Apnea Hypopnea Syndrome: does adherence to CPAP treatment improve glycemic control? *Sleep Med* 2009; 10: 887-891

Wei CY, Wang HL, Li J, Dong XS, An P, Ji LN, Wang F, Han F. [Effect of continuous positive airway pressure upon 24 h changes of blood glucose level in patients with obstructive sleep apnea hypopnea syndrome and type 2 diabetes]. *Zhonghua Yi Xue Za Zhi* 2009; 89: 2686-2689

Oktay B, Akbal E, Firat H, Ardic S, Kizilgun M. CPAP treatment in the coexistence of obstructive sleep apnea syndrome and metabolic syndrome, results of one year follow up. *Acta Clin Belg* 2009; 64: 329-334

Lam JC, Lam B, Yao TJ, Lai AT, Ooi CG, Tam S, Lam KS, Ip MS. A randomised controlled trial of nasal continuous positive airway pressure on insulin sensitivity in obstructive sleep apnea. *Eur Respir J* 2010; 35: 138-145

Garcia JM, Sharafkhaneh H, Hirshkowitz M, Elkhateib R, Sharaifkhaneh A. Weight and metabolic effects of CPAP in obstructive sleep apnea patients with obesity. *Respir Res* 2011; 12: 80

Shpirer I, Rapoport MJ, Stav D, Elizur A. Normal and elevated HbA1C levels correlate with severity of hypoxemia in patients with obstructive sleep apnea and decrease following CPAP treatment. *Sleep Breath* 2012; 16: 461-466