

Normal and elevated HbA1C levels correlate with severity of hypoxemia in patients with obstructive sleep apnea and decrease following CPAP treatment

Isaac Shpirer · Micha J. Rapoport · David Stav · Arnon Elizur

Received: 27 January 2011 / Revised: 31 March 2011 / Accepted: 26 April 2011 / Published online: 11 May 2011
© Springer-Verlag 2011

Abstract

Purpose Sleep apnea is associated with higher HbA1C levels in patients with and without diabetes but whether its severity correlates with HbA1C levels ranging from normal to abnormal is less clear. Also, the effect of continuous positive airway pressure (CPAP) treatment on HbA1C levels in patients with sleep apnea is controversial.

Methods Thirty consecutive patients with obstructive sleep apnea were studied. None of the patients was previously diagnosed with diabetes. All patients underwent overnight polysomnography and HbA1C levels were determined. Patients were subdivided into three groups according to their HbA1C levels: <6% ($n=10$), 6–6.5% ($n=10$), and $\geq 6.5\%$ ($n=$

10). Polysomnography and determination of HbA1C level were repeated in patients with severe sleep apnea ($n=12$) following 3–5 months of CPAP treatment.

Results HbA1C levels across the spectrum from normal to abnormal correlated with severity of hypoxemia (average SpO_2 , $r=-0.43$, $p=0.019$ and percent time with $SpO_2 < 90\%$, $r=0.48$, $p=0.007$). HbA1C levels decreased from a mean of $6.47 \pm 0.67\%$ to a mean of $6.28 \pm 0.51\%$, $p=0.038$ in 12 patients with severe sleep apnea following 3–5 months of CPAP treatment.

Conclusions The severity of hypoxemia in patients with sleep apnea correlates with HbA1C levels ranging from normal to pre-diabetes and diabetes. CPAP treatment for 3–5 months decreases HbA1C levels in patients with severe sleep apnea.

Keywords CPAP · Diabetes · HbA1C · Hypoxemia · Sleep apnea

I. Shpirer · D. Stav
The Institute of Pulmonary Medicine,
Assaf Harofeh Medical Center
(affiliated to the Sackler Faculty of Medicine,
Tel Aviv University),
Zerifin 70300, Israel

A. Elizur (✉)
Department of Pediatrics, Assaf Harofeh Medical Center
(affiliated to the Sackler Faculty of Medicine,
Tel Aviv University),
Zerifin 70300, Israel
e-mail: elizura@gmail.com

I. Shpirer · A. Elizur
The Sleep Laboratory, Assaf Harofeh Medical Center
(affiliated to the Sackler Faculty of Medicine,
Tel Aviv University),
Zerifin 70300, Israel

M. J. Rapoport
Department of Internal Medicine “C” and Diabetes Unit, Assaf
Harofeh Medical Center
(affiliated to the Sackler Faculty of Medicine,
Tel Aviv University),
Zerifin 70300, Israel

Introduction

Obstructive sleep apnea (OSA) is a state characterized by repetitive episodes of upper airway obstruction during sleep. It is accompanied by frequent arousals and repeated drops in oxygen saturation. OSA has been reported in recent years as part of the metabolic syndrome and is associated with obesity, dyslipidemia, and hypertension [1, 2].

Several studies have shown that OSA correlates with glucose intolerance and type 2 diabetes mellitus [3–5]. For example, it was demonstrated, using an oral glucose tolerance test, that the degree of OSA and the severity of hypoxemia are associated with glucose intolerance and increased risk of diabetes independent of BMI [6, 7]. It was

also found that the strongest parameter associated with impaired glucose tolerance in patients with OSA is the time spent at an oxygen saturation of $<90\%$ [8]. HbA1C levels were recently found to be similarly associated with a risk of diabetes and more strongly associated with a risk of cardiovascular disease or death of any cause compared to glucose intolerance [9]. This increased risk is evident at HbA1C levels equal to or greater than 6% and increases with levels equal to or greater than 6.5%. It is therefore of interest to examine the association between glycated hemoglobin and OSA. Several investigators found a correlation between OSA severity and HbA1C levels in patients with and without diabetes [10–13]. However, whether OSA correlates with HbA1C at levels ranging from normal to those posing increased risk of diabetes and cardiovascular disease is unknown. Our goal was to examine the correlation between OSA severity and a continuum of HbA1C levels. Therefore, we focused on patients without a previous diagnosis of diabetes whose HbA1C levels ranged from normal to abnormal.

Continuous positive airway pressure (CPAP) is the treatment of choice for most patients with sleep apnea but its effect on glucose metabolism in patients with OSA is controversial. While some authors have found that 3 months of CPAP has a beneficial effect on glucose levels measured continuously in diabetic patients and on HbA1C in a subset of these patients, others could not demonstrate a similar effect [14, 15]. A recent study did not find improvement in glucose metabolism after 6 weeks of CPAP in nondiabetic patients [16]. These conflicting results may be due to the fact that multiple factors other than sleep apnea can affect HbA1C levels and raise the question whether CPAP could improve glucose control in a subset of patients with OSA. In the current study, we examined the effect of 3–5 months of CPAP on HbA1C levels in patients with severe OSA. We speculated that in patients with a more severe disease, the effect of sleep apnea on HbA1C levels would be maximal, and therefore, the effect of CPAP would be substantial.

Methods

Patients

In a prospective cohort study, consecutive patients diagnosed with obstructive sleep apnea at Assaf Harofeh Medical Center's Sleep Laboratory during the years 2005–2007 were identified. Patients were included based on age (30–60 years old) and the presence of obstructive sleep apnea (apnea–hypopnea index $>5/h$). This study is part of a larger scale study examining the metabolic effects of sleep apnea. Overall, 47 patients entered the study. Fifteen patients with previously diagnosed diabetes or treated with

hypoglycemic medications were excluded. Two additional patients were excluded because of difficulties in drawing blood. The remaining 30 patients were analyzed. Informed consent was obtained from each patient included in the study and the study protocol was approved by the institution's human research committee. The study was registered as a clinical trial NCT00730873 at "clinicaltrials.gov".

Study protocol

All patients underwent a standard in-laboratory, overnight polysomnography, using a computerized polysomnography system (Embla; Flaga Medical; Reykjavik, Iceland), with the following channels: electroencephalography (C3-A2 and O2-A1), electrooculogram (right and left), chin electromyogram, arterial oxygen saturation, nasal pressure, electrocardiogram, chest and abdominal wall motion, bilateral tibialis electromyogram, and body position. The polysomnography recordings were scored manually for REM sleep stages, non-REM stages (stages 1, 2, 3, and 4), and for respiratory events (apnea/hypopnea), according to the American Academy of Sleep Medicine criteria [17–19]. Hypopnea was defined as a 10-s airflow reduction $>50\%$ of baseline or a reduction $>30\%$ with $\geq 4\%$ oxygen desaturation. Scoring was performed by a single blinded experienced scorer. Following polysomnography, routine laboratory tests were performed. Patients with severe sleep apnea (apnea–hypopnea index (AHI) ≥ 30) were treated with CPAP. Auto-titration was performed during overnight polysomnography using a portable system (Autotest, ResMed, Sydney, Australia). Optimal pressure was determined by analyzing the pressure that included 90% of the events with a leak lower than 0.4 l/s. CPAP usage time was electronically downloaded to assess adherence to treatment (defined as the average of at least 4 h of CPAP per night during the study period). After 3–5 months, these patients underwent repeated evaluation. The analysis of HbA1C levels both at baseline and following CPAP treatment was performed at the end of the study. Patients were divided, based on their baseline HbA1C levels, into three groups: nondiabetic ($n=10$) with HbA1C $<6\%$, pre-diabetic ($n=10$) with HbA1C level between 6.0% and 6.5%, and undiagnosed diabetic patients ($n=10$) with HbA1C levels equal to or greater than 6.5%.

Statistical analysis

Analyses were performed using SPSS 16.0 for Windows. Fisher's exact test was used to analyze the relationship between categorical variables, and the unpaired Student's *t* test was used to analyze the relationship between continuous variables. Pearson's correlation coefficient was used to analyze the correlation between continuous variables. Values

are expressed as means \pm standard deviation unless otherwise stated. A p value <0.05 was considered significant.

Results

Elevated HbA1C levels are commonly found in patients with OSA

None of the 30 patients consecutively recruited to the study was previously diagnosed as a pre-diabetic or diabetic patient. Nevertheless, only a third of these patients had HbA1C levels at the normal range, i.e., less than 6%, and the other two thirds had abnormal HbA1C levels posing increased risk for diabetes or cardiovascular disease and death. Of these, 10 had levels between 6% and 6.5% and 10 patients had levels equal to or greater than 6.5%. There were no significant differences in BMI or in biochemical parameters between the three groups (Table 1). Severe sleep apnea was found in 80% of the patients with HbA1C levels greater than 6.5% compared to 50% and 60% in patients with HbA1C $<6\%$ and those with HbA1C levels between 6% and 6.5%, respectively, but differences in OSA severity between the three groups were not statistically significant. There was a trend towards worse indices of hypoxemia with increasing levels of HbA1C but statistical significance was not met.

Hypoxemia correlates with HbA1C levels ranging from normal to abnormal in patients with sleep apnea

We next used Pearson's correlation to examine whether an association could be found between OSA severity and the continuum of HbA1C levels from normal to abnormal. A

significant correlation was found between parameters of hypoxemia, specifically the average SpO₂ ($r=0.65$, $p=0.019$) and the time spent with oxygen saturation $<90\%$ ($r=0.69$, $p=0.007$), and HbA1C levels (Fig. 1a, c). Because each of the two parameters, average SpO₂ and time spent with SpO₂ $<90\%$ is predicted by the other (they have collinearity), no significant correlations are found on multiple regression analysis, although the time spent with SpO₂ $<90\%$ seems to be the important one ($p=0.12$) compared to the average SpO₂ ($p=0.36$) in predicting HbA1C levels. Two additional parameters of hypoxemia, namely, the lowest SpO₂ reached during hypoxic episodes ($p=0.075$) and the average drop in SpO₂ during a desaturation event ($p=0.068$), showed similar trends in correlation to HbA1C levels but did not reach statistical significance (Fig. 1b, d). In contrast, HbA1C levels were not found to be in correlation with age ($p=0.19$), BMI ($p=0.26$), or lipid profile—triglycerides ($p=0.54$) and cholesterol ($p=0.41$).

CPAP improves HbA1C levels in patients with severe OSA

The effect of CPAP on HbA1C levels in patients with severe sleep apnea was then evaluated. Of the 30 patients included in the study, 19 had severe sleep apnea (AHI ≥ 30). These patients were followed for 3–5 months following the administration of CPAP. Five patients did not return for follow-up, and two patients who were followed were not compliant with CPAP and were therefore excluded. The remaining 12 patients were compliant with at least 4 h of CPAP per night. Three patients had normal HbA1C levels at the beginning of the study, three patients had levels between 6% and 6.5%, and six patients had HbA1C levels equal to or greater than 6.5%. When examined 3–5 months following the administration of CPAP, nine patients had lower HbA1C

Table 1 Comparison of patients based on HbA1C levels

Parameter		HbA1C <6 ($n=10$)	6 \leq HbA1C <6.5 ($n=10$)	HbA1C ≥ 6.5 ($n=10$)	p value	
Demographic	Age	53.7 \pm 6.3	54.5 \pm 8.5	52.1 \pm 9.7	0.8	
	Male gender	9 (90%)	9 (90%)	9 (90%)	1.0	
	BMI	31.5 \pm 5.0	32.5 \pm 4.9	34.8 \pm 5.0	0.32	
Biochemical	HbA1C%	5.7 \pm 1.7	6.1 \pm 0.1	6.9 \pm 0.4	<0.001	
	Triglycerides	165.9 \pm 116.1	158.5 \pm 60.4	178.1 \pm 65.5	0.87	
	Cholesterol	195.5 \pm 38.1	157.3 \pm 32.7	178.5 \pm 31.2	0.06	
Sleep-related	OSA severity	Mild	1 (10%)	2 (20%)	2 (20%)	0.39
		Moderate	3 (30%)	3 (30%)	0	
		Severe	6 (60%)	5 (50%)	8 (80%)	
	AHI		43.1 \pm 23.6	44.6 \pm 30.9	57.3 \pm 25.7	0.45
	Average SpO ₂ %		92.8 \pm 2.5	92.0 \pm 3.0	89.8 \pm 4.1	0.14
	Lowest SpO ₂ %		69.2 \pm 12.4	72.3 \pm 12.0	61.1 \pm 8.9	0.09
	SpO ₂ $<90\%$ (% time)		15.7 \pm 14.4	19.2 \pm 20.0	38.6 \pm 29.2	0.06
Average desaturation %		8.3 \pm 2.7	8.0 \pm 4.0	11.0 \pm 2.9	0.09	

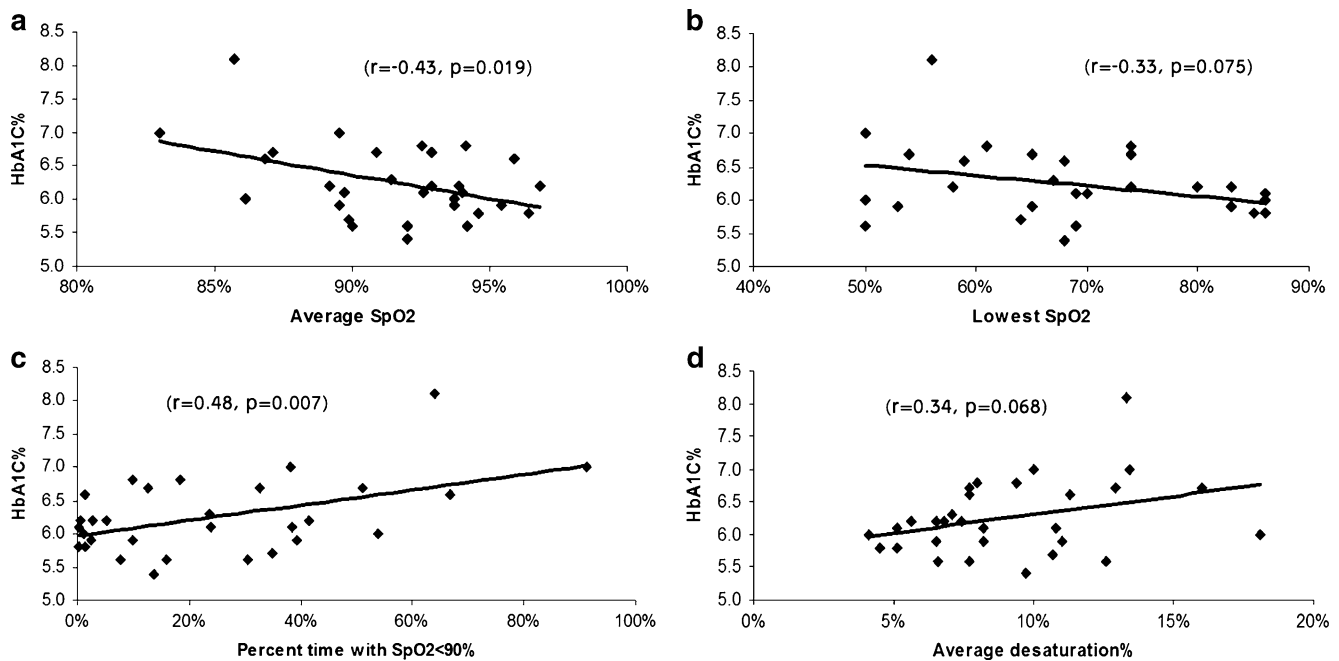


Fig. 1 Hypoxemia correlates with HbA1C levels in patients with OSA. Patients underwent overnight polysomnography and HbA1C levels were measured. Pearson correlation coefficient was used to

determine the correlation between the average SpO₂ (a), lowest SpO₂ (b), percent time with SpO₂<90% (c), and average desaturation % (d) and between HbA1C levels

levels, one patient (with a baseline HbA1C level of 6.1%) had an unchanged HbA1C level, and two patients had higher HbA1C levels compared to baseline (5.6% and 6.2% at baseline vs. 5.8% and 6.4%, respectively, at the end of the study). Average HbA1C levels of the entire group declined from a mean of $6.47 \pm 0.67\%$ to a mean of $6.28 \pm 0.51\%$ ($p = 0.038$) (Fig. 2). During the same time, there was no significant change in the patients' lipid profile or their BMI (data not shown).

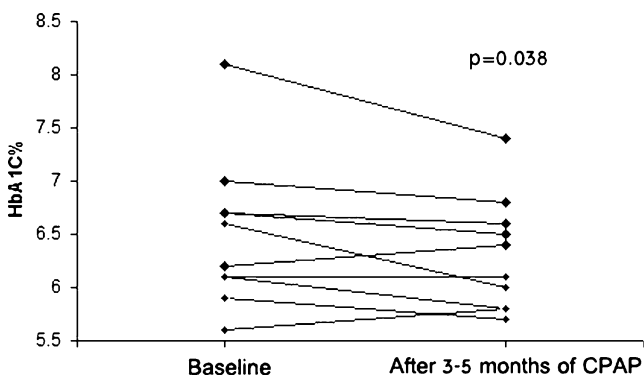


Fig. 2 HbA1C levels improve significantly in patients with severe OSA following 3–5 months of CPAP. HbA1C levels were measured in patients with severe OSA (AHI \geq 30) who were compliant (\geq 4 h of CPAP per night) with 3–5 months of CPAP. A paired Student's *t* test was used to compare the change in HbA1C levels before and after treatment

Discussion

In the present study, we demonstrate that hypoxemia in patients with sleep apnea correlates with HbA1C levels ranging from normal to pre-diabetic and diabetic range. A significant reduction in HbA1C levels was found in patients with severe sleep apnea who were compliant with 3–5 months of CPAP.

We found that two major parameters of hypoxemia, namely, the average SpO₂ and the percent time spent with SpO₂<90%, were significantly associated with HbA1C levels in the entire group of patients. Data derived from animal models indicate that a correlation exists between parameters of hypoxemia and glucose intolerance [20, 21]. Clinical studies have shown that the prevalence of diabetes is markedly higher in patients with sleep apnea compared to controls [4, 5] and that sleep apnea is independently associated with insulin resistance in patients without known diabetes [22, 23]. However, only a few studies examined the association between sleep apnea and HbA1C levels. HbA1C levels in patients with type 2 diabetes were found to be associated with sleep apnea severity and with indices of hypoxemia [12, 13]. In patients without diabetes, increased HbA1C levels were associated with higher AHI. However, HbA1C levels were below 6% in all patients, even in those with more severe sleep apnea. In addition, a simplified rather than a full polysomnography was used in this study to determine OSA severity [10]. Another study

that demonstrated a correlation between HbA1C levels and the severity of sleep-disordered breathing included males only and excluded patients with HbA1C >6.5% [11]. We extend these observations as we examined patients across a continuum of HbA1C levels. We demonstrate that HbA1C levels ranging from 5.6% to 8.1% correlate with the degree of hypoxemia. These findings are of particular importance as HbA1C levels $\geq 6\%$, and to a greater degree $\geq 6.5\%$, were recently shown to be similarly associated with a risk of diabetes and to be better predictors of cardiovascular disease and death in nondiabetic adults compared with fasting glucose [9].

We found that more than two thirds of the patients in our study, who were not previously diagnosed as pre-diabetic or diabetic, had HbA1C levels $\geq 6\%$ and a third had levels $\geq 6.5\%$. These findings match descriptions elsewhere. In one study that examined glucose intolerance using a 2-h OGTT, type 2 diabetes was diagnosed in 30.1% and impaired glucose tolerance in an additional 20% of 595 men with sleep apnea that were not previously diagnosed with diabetes [23]. In another study, in 24 patients with OSA and without diabetes, 79.2% were found to have glucose intolerance and 25% had diabetes [24]. Our findings extend these observations by demonstrating poor glycemic control over time in patients with OSA.

In addition, we demonstrate that adherence to 3–5 months of CPAP significantly reduces HbA1C levels in patients with severe OSA. CPAP is the treatment of choice for most patients with obstructive sleep apnea, but the effect of CPAP therapy on insulin resistance and on the levels of glycated hemoglobin in patients with OSA is controversial. West et al. have demonstrated no significant improvement in glycemic control and in insulin resistance in diabetic patients with OSA following 3 months of CPAP [14]. In contrast, Steiropoulos et al. were able to show a significant decline in HbA1C levels in sleep apnea patients without known diabetes following 6 months with CPAP [25]. Our study group is different from the above in that it contains patients with abnormal baseline HbA1C levels and severe OSA but without a previous diagnosis of diabetes. It could be that HbA1C levels are affected by CPAP only in a subgroup of patients with severe sleep apnea, and this may account for the contradictory findings in different studies. Furthermore, the improvement in HbA1C levels in these patients suggests that CPAP may be a valuable treatment modality equivalent to lifestyle changes or addition of metformin which are usually indicated in these circumstances [26].

This study has several limitations. We used a single night of PSG to determine sleep apnea severity. As there may be night-to-night variability, this may affect our results [27]. There is no reason to assume, however, that this effect would be in a direction not in favor of our results. In

addition, as the study was performed from 2005 to 2007, patients were diagnosed by the AASM 1999 criteria. Due to difficulties in blinding the studies once they were open to the scorers, we did not score them again based on the AASM 2007 criteria. Regardless, the new scoring system would not have changed parameters of hypoxemia and therefore would not have altered the main findings of the study, namely, the association between hypoxemia and HbA1C levels.

In summary, in this study, we demonstrate that in patients with OSA, hypoxemia correlates with HbA1C levels across a continuum ranging from normal to levels posing increased risk for diabetes, cardiovascular disease, and death. Elevated HbA1C levels, in patients with severe OSA, improve following 3–5 months of treatment in those who are compliant with CPAP. Future studies will determine the efficacy of this treatment modality in improving long-term glucose control in these patients.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Vgontzas AN, Bixler EO, Chrousos GP (2005) Sleep apnea is a manifestation of the metabolic syndrome. *Sleep Med Rev* 9:211–224
2. Shpirer I, Copel L, Broide E, Elizur A (2010) Continuous positive airway pressure improves sleep apnea associated fatty liver. *Lung* 188(4):301–307
3. Tasali E, Mokhlesi B, Van Cauter E (2008) Obstructive sleep apnea and type 2 diabetes: interacting epidemics. *Chest* 133(2):496–506
4. West SD, Nicoll DJ, Stradling JR (2006) Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax* 61(11):945–950
5. Reichmuth KJ, Austin D, Skatrud JB, Young T (2005) Association of sleep apnea and type II diabetes: a population-based study. *Am J Respir Crit Care Med* 172(12):1590–1595
6. Punjabi NM, Sorkin JD, Katznel LI, Goldberg AP, Schwartz AR, Smith PL (2002) Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 165(5):677–682
7. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE, Sleep Heart Health Study Investigators (2004) Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol* 160(6):521–530
8. Sulit L, Storer-Isser A, Kirchner HL, Redline S (2006) Differences in polysomnography predictors for hypertension and impaired glucose tolerance. *Sleep* 29(6):777–783
9. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL (2010) Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 362(9):800–811
10. Okada M, Takamizawa A, Tsushima K, Urushihata K, Fujimoto K, Kubo K (2006) Relationship between sleep-disordered breathing and lifestyle-related illnesses in subjects who have undergone health-screening. *Intern Med* 45(15):891–896

11. Papanas N, Steiropoulos P, Nena E, Tzouveleakis A, Maltezos E, Trakada G, Bouros D (2009) HbA1c is associated with severity of obstructive sleep apnea hypopnea syndrome in nondiabetic men. *Vasc Health Risk Manag* 5:751–756
12. Aronsohn RS, Whitmore H, Van Cauter E, Tasali E (2010) Impact of untreated obstructive sleep apnea on glucose control in type 2 diabetes. *Am J Respir Crit Care Med* 181(5):507–513
13. Steiropoulos P, Papanas N, Bouros D, Maltezos E (2010) Obstructive sleep apnea aggravates glycemic control across the continuum of glucose homeostasis. *Am J Respir Crit Care Med* 182(2):286
14. West SD, Nicoll DJ, Wallace TM, Matthews DR, Stradling JR (2007) Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. *Thorax* 62(11):969–974
15. Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T (2005) Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. *Arch Intern Med* 165(4):447–452
16. Coughlin SR, Mawdsley L, Mugarza JA, Wilding JP, Calverley PM (2007) Cardiovascular and metabolic effects of CPAP in obese males with OSA. *Eur Respir J* 29(4):720–727
17. Rechtschaffen A, Kales A (1968) A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. UCLA Brain Information Service/Brain Research Institute, Los Angeles
18. Association American Sleep Disorders (1992) EEG arousals: scoring rules and examples. A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 15(2):173–184
19. American Academy of Sleep Medicine Task Force (1999) Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 22:667–689
20. Polotsky VY, Li J, Punjabi NM, Rubin AE, Smith PL, Schwartz AR, O'Donnell CP (2003) Intermittent hypoxia increases insulin resistance in genetically obese mice. *J Physiol* 552:253–264
21. Iiyori N, Alonso LC, Li J, Sanders MH, Garcia-Ocana A, O'Doherty RM, Polotsky VY, O'Donnell CP (2007) Intermittent hypoxia causes insulin resistance in lean mice independent of autonomic activity. *Am J Respir Crit Care Med* 175:851–857
22. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS (2002) Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 165:670–676
23. Meslier N, Gagnadoux F, Giraud P, Person C, Ouksel H, Urban T, Racineux JL (2003) Impaired glucose-insulin metabolism in males with obstructive sleep apnoea syndrome. *Eur Respir J* 22:156–160
24. Peltier AC, Consens FB, Sheikh K, Wang L, Song Y, Russell JW (2007) Autonomic dysfunction in obstructive sleep apnea is associated with impaired glucose regulation. *Sleep Med* 8(2):149–155
25. Steiropoulos P, Papanas N, Nena E, Tsara V, Fiteli C, Tzouveleakis A, Christaki P, Maltezos E, Bouros D (2009) 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* 10(8):887–891
26. (2010) Executive summary: standards of medical care in diabetes—2010. *Diabetes Care* 33 Suppl 1:S4–10
27. Ahmadi N, Shapiro GK, Chung SA, Shapiro CM (2009) Clinical diagnosis of sleep apnea based on single night of polysomnography vs. two nights of polysomnography. *Sleep Breath* 13(3):221–226