Treatment with Continuous Positive Airway Pressure May Affect Blood Glucose Levels in Nondiabetic Patients with Obstructive Sleep Apnea Syndrome

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Study Objectives: Obstructive sleep apnea syndrome (OSAS) is often associated with impaired glucose metabolism. Data on the effects of OSAS treatment with continuous positive airway pressure (CPAP) on blood glucose and insulin resistance are conflicting. The study aimed at assessing the immediate effect of CPAP on glucose control measured with a continuous glucose monitoring system (CGMS).

Participants and Measurements: Nine non-diabetes subjects with OSAS (mean age 53.0 ± 8.0 years; body mass index 34.8 ± 5.3 kg/m2) underwent 2 overnight polysomnographic examinations: a diagnostic study and one with CPAP treatment. Continuous glucose monitoring system (CGMS) was applied overnight on both occasions. Glucose metabolism was assessed with a 75-g oral glucose tolerance test, plasma insulin and homeostatic model assessment of insulin resistance (HOMA-IR) index.

Results: The mean (± SD) apnea-hypopnea index (AHI) at diagnostic polysomnography was 54.3 ± 29.3 (range 16-81). Fasting plasma insulin levels in patients with OSAS was 84.3 ± 43.4 pmol at baseline, and the HOMA-IR was 3.6 ± 2.2. CPAP treatment in the subjects with OSAS resulted in a significant reduction in the AHI to 4.5 ± 7.1. All of the major saturation parameters improved significantly on CPAP. CGMS showed mean glucose values significantly higher during the CPAP night than during the diagnostic night: 80 ± 11 mg/dL versus 63 ± 7 mg/dL (P < .01). Fasting insulin and HOMA-IR measured after the CPAP night tended to be higher than at baseline (88.4 ± 51.0 pmol vs 84.3 ± 43.4 pmol and 3.9 pmol ± 2.6 vs 3.6 ± 2.2 pmol, respectively, P > .05).

Conclusion: CPAP treatment in nondiabetic obese patients with OSAS may have an immediate elevating effect on blood glucose.

Key Words: Insulin resistance, obesity, growth hormone, obstructive sleep apnea syndrome, continuous positive airway pressure (CPAP), continuous glucose monitoring system (CGMS)

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INTRODUCTION

OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS) HAS BEEN REPEATEDLY SHOWN TO BE ASSOCIATED WITH IMPAIRED GlUCOSE METABOLISM, RESULTING MAINLY FROM INSULIN RESISTANCE.1-3 and, more recently, OSAS has been linked to the metabolic syndrome.4 However, data on early or late effects of OSAS treatment with continuous positive airway pressure (CPAP) on blood glucose and insulin resistance are conflicting.5,6,9 We have therefore conducted a study aiming to assess the immediate effect of CPAP on glucose control measured with a continuous glucose monitoring system (CGMS).10

The CGMS is a recently developed electronic system designed to continuously monitor subcutaneous glucose concentration in interstitial fluid. It consists of 4 elements: a subcutaneous glucose sensor, a pager-sized continuous glucose monitor worn on a belt, a cable, and a communication station with software. A disposable sterile 1-cm needle-like glucose sensor is inserted into the subcutaneous tissue 15 to 20 cm laterally from the umbilicus. The glucose sensor records interstitial glucose concentration every 10 seconds and stores an average glucose value for each 5-minute period, thus enabling up to 288 measurements to be made per day. The sensor measures glucose as a potential, created by the chemical reaction in which hydrogen peroxide is formed by glucose oxidase from glucose and oxygen. The sensor requires calibration to be made at least 4 times during each day that the CGMS is used. The sensor is calibrated by entering the blood glucose measurement obtained from a glucose meter into the monitor. The CGMS is designed to record glucose levels for up to 72 hours, and it reliably measures glucose concentrations in the range of 40 to 400 mg/dL.10,11 Within normal glucose values, the correlation coefficient between the CGMS results and the readings on the blood glucose meters have been reported to be between 0.84 and 1.0, and mean absolute error to be from 7% to 17%.11 Boyne et al12 found that in a group of patients with type 1 diabetes who experienced blood glucose levels between 50 and 250 mg/dL, the interstitial glucose may lag behind blood glucose for 4 to 10 minutes, usually when rapid changes in blood glucose occur. This observation, however, is not relevant for persons with normal glucose metabolism who maintain stable blood glucose levels.

METHODS

Nine subjects without diabetes with clinical diagnosis of OSAS (7 men, 2 women; mean age 53.0 ± 8.0 years; body weight 101.9 ± 18.5 kg; body mass index 34.8 ± 5.3 kg/m2) underwent 2 overnight polysomnographic examinations (Erich Jaeger, Hoechberg, Germany), a diagnostic study and one with CPAP treatment. Pressures were titrated in all patients with auto-CPAP (AutoSet Spirit, ResMed, Australia) with standard settling of 30 minutes and basal positive airway pressure of 4 or 5 mbar. Those periods with low constant pressure (‘settling’) were to enable a patient to

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fall asleep and were not included in the calculation of the apneahypopnea index (AHI). All CPAP pressures were obtained from the mask gauge connected to the pressure transducer in the yoke box, which was calibrated with the external CPAP device from 0 to 20 mbar. For all the patients in the study, the standard nasal CPAP was applied. Partial response was observed in only 1 patient (CPAP AHI = 22) and that was because of too low an upper-limit setting on the autodevice. The standard range of pressure settings on the auto-CPAP was from 4 or 5 to 14 mbar.

All the patients had continuous glucose monitoring (CGMS, MiniMed, Northridge, Calif, USA) applied overnight on both occasions (7.2 ± 0.5 and 6.9 ± 0.8 hours of recording, respectively). In each patient, the CGMS monitor was calibrated 4 times during each night: 1 minute before and 4 hours and 3 hours after the monitor was turned on and 1 minute before it was turned off.19

At baseline, all subjects had a 75-g oral glucose tolerance test performed. Fasting plasma insulin was assessed at baseline and after the CPAP night (ELISA, reagents from DAKO, Ely, UK, reference range 10.8-85.8 pm). The homeostatic model assessment of insulin resistance (HOMA-IR) index was used to assess each patient’s insulin resistance. The HOMA-IR was calculated from fasting plasma glucose and insulin values measured in a single sample according to the formula insulin (expressed in mU/L) × glucose (mmol/L)/22.5.15 The HOMA-IR has been repeatedly shown to be a reliable indicator of insulin resistance (the greater the index value, the greater the insulin resistance).14

The patients were instructed to maintain their dietary habits during the study. All patients gave their written informed consent to participate in the study.

RESULTS

The mean (± SD) AHI at diagnostic polysomnography was 54.3 ± 29.3 (range 16-81), which confirmed a diagnosis of OSAS. We observed the rise in the basal hemoglobin saturation from 88.5% ± 5.1% (diagnostic night) to 92.6% ± 2.6% (CPAP night) (P < .05). All of the major saturation parameters improved significantly on CPAP titration. The index of desaturations (number of desaturations per total sleep time) was reduced 10-fold from 58 ± 29 to 6 ± 10. The mean saturation level for all desaturations below 90% increased from 81.7% ± 6.9% to 87.5% ± 2.6% (P < .01). Similarly, the minimum saturation value rose from 63.8% ± 13.8% to 82.1% ± 9.8% (P < .001). The T90% (the percentage of total sleep time spent below a saturation of 90%) was reduced 10-fold from 41% ± 22% to 4% ± 7% (P < .001).

Values on the oral glucose tolerance test were 101 ± 11, 187 ± 40, and 128 ± 59 mg/dL at 0, 60, and 120 minutes, respectively. Two patients had impaired glucose tolerance, while 7 presented with normal glucose metabolism. Fasting plasma insulin levels at all in subjects with a body mass index greater than 30 kg/m².

Increased insulin sensitivity was also found by Brooks et al in patients with type 2 diabetes after 4 months of CPAP treatment.6 Others have failed to note any effect of CPAP on glucose control,5,7,8 but some of these studies were methodologically flawed.6 Our study is, to the best of our knowledge, the first to report the influence of CPAP on glucose control assessed with CGMS.

It appears that significant improvement of AHI and oxygen saturation achieved with CPAP may have an immediate effect on blood glucose in subjects without diabetes. The increase in glucose levels that we noted may be explained by the reported increase in plasma growth hormone during CPAP treatment.15 Growth hormone exerts strong lipolytic effects, and its administration leads to an elevation in the plasma concentration of free fatty acids.16 As has been postulated by Randle et al,17 an increase in the supply of free fatty acids may decrease glucose utilization by skeletal muscles and thus cause hyperglycemia. This effect is typically observed in patients deficient in growth hormone, in whom treatment with growth hormone, in its early stage, enhances insulin resistance and leads to blood glucose elevation.17 Subjects with OSAS present with low growth-hormone levels, and, as shown by Cooper et al,7 CPAP treatment causes significant increases in growth-hormone levels, which lead to an elevation in plasma free fatty acids and 3-hydroxybutyrate, the products of growth hormone-stimulated lipolysis.

Still, it may be argued that other CPAP effects on sympathetic nervous system activity or skeletal muscle activity may affect blood glucose. Heitmann et al18 reported that long-term CPAP treatment (ie, for a mean of 7 weeks) may indeed reduce sympathetic activity by one-third, which in turn may be expected to reduce blood glucose fullstop. In our study, however, we were assessing the immediate effect of CPAP on blood glucose, and, even if sympathetic nervous system activity was effectively inhibited in our patients as a result of improved oxygen saturation and thus had a lowering effect on blood glucose, the actual increase in glucose values might have been even greater than was noted by CGMS.

Skeletal muscle activity is difficult to assess in the standard polysomnogram because there is no reliable method to measure muscular activity. Submandibular electromyography with superficial disk electrodes is conducted for the purpose of sleep staging (rapid eye movement assessment). Periodic limb movements...
reflect the activity of only 1 muscle group (peroneal muscles) and are prone to various artifacts (variable conductivity of the skin, compression, from leg crossing). However, decreased skeletal muscle activity associated with improvement in sleep function is unlikely to cause any significant increase in blood glucose, let alone by as much as 27%. In individuals without diabetes, glucose metabolism and plasma glucose levels are under sensitive and tight hormonal control, which can easily respond to changes in muscle activity.19

We noted a significant correlation between the severity of OSAS (as expressed in saturation parameters) and insulin resistance, as well as fasting plasma glucose, a parameter more affected by insulin resistance rather than dysfunction in insulin secretion. Interestingly, no such association was found for post-challenge plasma glucose or CGMS glucose measurements, which indicates that insulin resistance is particularly closely related to OSAS, a finding already reported by Punjabi et al17 and Ip et al.20 A postulated increase in the release of growth hormone may additionally worsen already poor insulin sensitivity in patients with OSAS. Should this assumption be correct, it may lead to a paradoxical situation: insulin-resistant subjects have more severe OSAS, and, when treated with CPAP, their insulin resistance might actually increase due to CPAP-induced hormonal changes. Obviously, the interpretation of our findings must be done with caution because of the relatively small number subjects enrolled; further studies are therefore urgently needed to shed more light on the effects of CPAP treatment on glucose metabolism in patients with OSAS who are already insulin resistant.

CONCLUSION

CPAP treatment in nondiabetic obese patients with OSAS may have an immediate elevating effect on blood glucose, which could be the result of plausible hormonal and metabolic changes (increased growth hormone-stimulated lipolysis) related to improved ventilation and sleep structure, as well as to preexistent insulin resistance. As a practical application of our findings, this should be taken into account when diagnosing glucose metabolism disorders in subjects with OSAS in the initial period of CPAP treatment.

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