Sleep Medicine Reviews xxx (2015) 1–10

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Effects of continuous positive airway pressure treatment on glucose metabolism in patients with obstructive sleep apnea

Elisabet Martínez-Ceron [a], Isabel Fernández-Navarro [a], Francisco Garcia-Rio [a, b, c, *]

[a] Servicio de Neumología, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain
[b] Universidad Autónoma de Madrid, Madrid, Spain
[c] CIBER de Enfermedades Respiratorias-CIBERES, Madrid, Spain

ARTICLE INFO

Article history:
Received 28 January 2015
Received in revised form
9 March 2015
Accepted 23 March 2015
Available online xxx

Keywords:
Sleep
Sleep apnea
Diabetes
Continuous positive airway pressure
Glucose
Insulin

SUMMARY

A possible association between obstructive sleep apnea (OSA) and type 2 diabetes (T2DM) has been suggested. OSA could alter glucose metabolism, generating insulin resistance and favoring the development of T2DM. In addition, our greater understanding of intermediate disorders produced by intermittent hypoxia and sleep fragmentation, such as sympathetic activation, oxidative stress, systemic inflammation and alterations in appetite-regulating hormones, provides biological plausibility to this possible association. Nevertheless, there are still few data available about the consequences of suppressing apnea. Therefore, the objective of this review was to analyze current knowledge about the effect of continuous positive airway pressure (CPAP) on glucose metabolism.

A global interpretation of the studies evaluated shows that CPAP could improve insulin resistance, and perhaps also glycemic control, in OSA patients who still have not developed diabetes. In addition, it seems possible that the effect of CPAP is still greater in patients with OSA and T2DM, particularly in those patients with more severe and symptomatic OSA, in those with poorer baseline glycemic control and with greater compliance and duration of CPAP treatment.

In conclusion, although the current information available is limited, it suggests that apnea reversion by means of CPAP could improve the control of glucose metabolism.

Introduction

Continuing evidence suggests the existence of a relationship between obstructive sleep apnea (OSA) and several metabolic disorders, particularly type 2 diabetes (T2DM) [1–3]. Some clinical-epidemiological data argue that OSA can alter glucose metabolism, progressing from increased insulin resistance [4] to glucose intolerance [5], poor metabolic control of glycemia [6,7], and the development of T2DM [8]. Furthermore, OSA could also aggravate the evolution of T2DM [9–13]. In fact, glycosylated hemoglobin (HbA1c) has been reported to increase 1.49% in patients with mild OSA, 1.93% in moderate OSA and 3.69% in severe OSA when compared with control subjects [12]. In addition, other measurements of OSA severity, such as the apnea-hypopnea (AHI) and oxygen desaturation (ODI) indices during REM sleep, are also related with the concentration of HbA1c [12].

Our better understanding of the repercussions of pathophysiological disorders caused by OSA in glucose metabolism provides the OSA-T2DM correlation with grounds for biological plausibility. Schematically, OSA is thought to activate two triggering mechanisms (intermittent hypoxia and sleep fragmentation) that induce several intermediate disorders, such as sympathetic nervous system activation, oxidative stress, systemic inflammation, alterations in appetite-regulating hormones and activation of the hypothalamic-pituitary-adrenal axis, which favor the development of insulin resistance and its progression towards glucose intolerance and, ultimately, diabetes [3,14–21] (see Fig. 1).

To complete the assessment of the OSA-T2DM association, it is important to consider the role of CPAP treatment in glucose metabolism. Consequently, the objective of this review is to analyze the state of our understanding of CPAP effect on glucose metabolism. The results should be interpreted with caution as most of the available evidence is based on uncontrolled studies (see Table 1), and controlled studies about the CPAP effect on glycemic

* Corresponding author. Alfredo Marquerie 11, izqda, 1° A, 28034-Madrid, Spain. Tel.: +34 917 300 170; fax: +34 912 071 061.
E-mail address: fgr01m@gmail.com (F. Garcia-Rio).

http://dx.doi.org/10.1016/j.smrv.2015.03.002
1087-0792/

Glossary of terms

AHI	apnea-hypopnea index
BMI	body mass index
CPAP	continuous positive airway pressure
DI	desaturation index
DM	diabetes mellitus
HbA1c	glycosylated hemoglobin
HOMA	homeostasis model assessment
OGTT	oral glucose tolerance test
OSA	obstructive sleep apnea
QUICKI	quantitative insulin sensitivity check index
RCT	randomized controlled trials
SITT	short insulin tolerance test
T2DM	type 2 diabetes mellitus

control are scarce (see Table 2). Furthermore, in order to better interpret the role of CPAP on metabolic control, it seems convenient to differentiate between studies done in OSA patients with and those without diabetes.

Studies in non-diabetic patients with sleep apnea

Several studies provide information about the effect of CPAP on the fasting glucose and insulin levels, insulin resistance and glycemic control of patients with OSA who still have not developed diabetes.

CPAP effect on fasting glucose and insulin levels

Although initial observational studies were not able to demonstrate any type of an effect [22,23], Chin et al. [24] provided the first evidence of a CPAP effect on carbohydrate metabolism. In their study, 22 obese patients with severe OSA underwent 6 mo of CPAP treatment. While the fasting insulin and glucose levels did not vary after CPAP therapy, glucose levels during the oral glucose tolerance test (OGTT) decreased significantly without any concomitant changes in insulin levels, except for insulin levels at 180 min. However, these changes were only significant in patients with weight loss during the treatment period [24], suggesting that this effect might depend on body weight.

Along the same lines, Henley et al. [25] demonstrated that CPAP seems to be especially effective in obese patients with severe OSA. By comparing the response to OGTT of 15 obese males with newly diagnosed severe OSA both before and after three months of CPAP, they recorded a reduction in fasting glucose and insulin levels as well as their respective areas under a the curve. From the analysis of circulating levels of apelin, an adipokine secreted from adipocytes with an important role in glucose homeostasis as well as cardiovascular physiology [26,27], these same authors make an interesting additional contribution by suggesting that weight loss may not be the mechanism by which insulin and glucose levels improve, but may instead be an indirect marker of the CPAP effect on insulin production. They find that untreated OSA patients have elevated plasma apelin levels, altered apelin secretory dynamics in response to oral glucose and lack of an apparent circadian variability, which was restored after three months of CPAP [25]. Usually, hyperinsulinemia is the main determinant of adipocyte apelin expression and secretion [26,28], which has a glucose-lowering effect associated with enhanced glucose utilization [29]. Thus, they proposed that the increased apelin plasma levels found in OSA patients represent an insulin-dependent up-regulation of apelin secretion to improve glucose utilization, whereas the post-CPAP down-regulation of apelin might only be justified by a primary amelioration of hyperinsulinemia secondary to CPAP [25].

In any case, it has also been shown that the effect of CPAP on plasma insulin levels is not exclusive of patients with severe OSA. In fact, in a sample of 28 patients with few symptoms and AHI $\geq$10 h^{-1} versus 28 control subjects, there was a greater reduction in fasting serum insulin in OSA patients than in the controls after three wk of CPAP treatment [30]. However, in these patients it is very difficult to maintain adequate CPAP compliance during prolonged periods of time. In fact, only 29% adequately completed six months of treatment [30].

The number of randomized controlled trials (RCT) evaluating the effect of CPAP on fasting insulin or glucose levels of OSA patients without diabetes is still limited. No effect on these levels has been demonstrated after one [31] or six wk of CPAP treatment [32]. Sivam et al. [33] evaluated 27 patients with moderate-severe OSA treated with 8 wk of CPAP versus sham CPAP and found no differences in fasting glucose or the distribution and amount of subcutaneous and visceral fat, which suggests that longer CPAP use might be necessary to show a difference. The most recent trial by Hoyos et al. [34] confirms the need for longer treatment periods. They evaluated the effect of 12 wk of CPAP or sham CPAP on glucose metabolism in 65 non-diabetic men with moderate-severe OSA who were CPAP naïve. With shorter CPAP use (3.6 h/day), there were no between-group differences at 12 wk in fasting glucose or insulin levels. However, when therapeutic CPAP was prolonged for an open-label period of another 12 wk, a reduction was detected in the fasting insulin levels of these patients [34].

CPAP effect on insulin resistance

In order to achieve an improvement in glucose metabolism control, it is necessary to reduce insulin resistance so that a lower production of insulin is required to maintain glucose homeostasis. The effect of CPAP on insulin resistance has been evaluated in different observational studies using the hyperinsulinemic-euglycemic clamp as well as the homeostatic model assessment-insulin (HOMA index), with varying results.

The impact of CPAP on insulin resistance has been a secondary variable in small observational studies aimed at analyzing the response after three months of CPAP on regional lipid deposition and appetite-regulating hormones in obese patients with OSA [35–37]. Although some studies detected a reduction in visceral adipose tissue and circulating leptin levels [35] or a reversion of hypoadiponectinemia [37], none detected a change in insulin resistance. Likewise, insulin resistance was also a secondary variable in observational studies with various sample sizes and follow-ups that showed a CPAP effect on the lipid profile [38], oxidative stress [39] or endothelial reactivity [40] of patients with OSA and different associated comorbidities. None of them identified a CPAP effect on insulin resistance.

Besides being a secondary objective, the lack of control of some variables (mainly obesity) could explain their negative results. In fact, another study with a pre-post within-subjects design, in which insulin and appetite-regulating hormones were assayed in 20 obese subjects with OSA, confirmed that change in body weight is the main determinant for insulin resistance in obese OSA patients [41]. Even though after six months of treatment no improvements in insulin resistance or leptin, adiponectin or resistin levels were observed, the authors reported that some patients experienced increased insulin resistance associated with weight gain during the study.

Please cite this article in press as: Martínez-Ceron E, et al., Effects of continuous positive airway pressure treatment on glucose metabolism in patients with obstructive sleep apnea, Sleep Medicine Reviews (2015), http://dx.doi.org/10.1016/j.smrv.2015.03.002