Continuous positive airway pressure to improve insulin resistance and glucose homeostasis in sleep apnea

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INTRODUCTION
Obstructive sleep apnea syndrome (OSAS) is a common disorder affecting approximately 3%-7% of adult men and 2%-5% of adult women in the general population[1]. OSAS is characterized by repeated episodes of complete or partial obstruction of the upper airway during sleep and is being increasingly recognized as an important cause of morbidity and mortality[1]. The main symptoms of OSAS are nocturnal respiratory pauses interrupted by loud snoring and excessive daytime sleepiness. Rapidly accumulating data from both epidemiological and clinical studies suggest that OSAS is independently associated with alterations in glucose metabolism and that it places patients at an increased risk for the future development of type 2 diabetes[2].

CONTINUOUS POSITIVE AIRWAY PRESSURE TO TREAT OSAS
Continuous positive airway pressure (CPAP) is the treatment of choice for OSAS[4]. It has proven to be efficacious in eliminating obstructive respiratory events during sleep and in improving sleep architecture, daytime sleepi-
ness and quality of life[13]. CPAP is commonly used to treat OSAS by delivering a constant pressure throughout inspiration and expiration to maintain upper airway patency during sleep. It consists of a flow generator that delivers airflow at a constant pressure to the patient through a mask via a tubing system. CPAP technology has improved considerably over the years. This technological progress notwithstanding, patient adherence to CPAP treatment remains suboptimal and its use during sleep time shows substantial variation between patients[13].

CONTINUOUS POSITIVE AIRWAY PRESSURE: ITS ROLE IN GLUCOSE HOMEOSTASIS

Not only is CPAP the established treatment for OSAS, it may also have a favorable effect on insulin resistance and glucose metabolism in such patients. It has been postulated that CPAP can ameliorate intermittent hypoxia and sympathetic overactivation, both pathophysiological mechanisms responsible for the impaired glucose metabolism in OSAS patients. This additional therapeutic benefit conferred by CPAP is now attracting considerable interest but is still an issue of ongoing debate[8]. Indeed, findings from numerous studies on the effect of CPAP treatment on glucose metabolism, both in diabetic and non-diabetic populations, have been rather conflicting. This can be attributed to differences between the studied populations (i.e. diabetic, non-diabetic, obese or non-obese patients), the primary outcomes, the method of assessment of glucose metabolism (i.e. fasting glucose, glycated hemoglobin, hyperinsulinemic euglycemic clamp etc.), the period of CPAP application (ranging between 1 night and 2.9 years)[8] and the patient’s adherence to CPAP use[9]. Unfortunately, only three randomised control studies have so far examined the effect of CPAP on different parameters of glucose metabolism[10-12] and only one, the most recent, has shown a favorable effect.

The latter[10] demonstrated an increase in insulin sensitivity among the 31 patients with moderate/severe OSAS who received CPAP treatment, as opposed to no improvement among the 30 controls receiving sham CPAP. An additional improvement was also recorded after 12 wk of CPAP use in subjects with body mass index exceeding 25 kg/m²[10]. The authors have used the short insulin tolerance test, a rapid and simple test that has been validated against clamp studies[13] and whose short duration inhibits interference from counter regulatory hormones[14]. Additional strengths of the study include good CPAP adherence and exclusion of OSA patients with comorbidities, a fact that allows a clear delineation of the impact of OSA per se on glucose metabolism.

Conversely, two further randomised control studies indicate that CPAP treatment does not improve glucose metabolism. The first one by West et al[11] compared 20 OSAS patients receiving automatic positive airway pressure (APAP) therapy with 22 OSAS patients receiving sham therapy for 3 mo (Table 1). All patients were male with established type 2 diabetes mellitus. There was no significant change in haemoglobin A1c (HbA1c), insulin sensitivity assessed by euglycemic clamp and HOMA in either group[11]. Even after excluding 8 patients with poor compliance, changes remained insignificant[11]. The other study by Coughlin et al[12] was a randomised placebo-controlled blinded cross-over trial, comparing 6 wk of therapeutic and sham CPAP in 34 obese OSAS patients. No change occurred in fasting glucose and insulin levels or insulin resistance, as assessed by HOMA[12]. Nonetheless, it should be borne in mind that the study period was rather short. Indeed, the authors themselves queried whether a prolonged longer study period would be necessary to reveal significant changes[13].

Clearly, the role of CPAP in the improvement of glucose metabolism and insulin sensitivity has not been defined yet[8]. Results are conflicting which may be explained by the differences in recruited populations (diabetic or non-diabetic), adherence to CPAP use, as well as in study design (duration of follow-up) and endpoints (different parameters of insulin resistance and glucose homeostasis)[8]. In addition, other issues such as the role of diet and exercise should always be addressed.

CONCLUSIONS AND FUTURE DIRECTIONS

In the light of current knowledge, further research therefore needs to revisit the effect of CPAP on glucose homeostasis[8]. It is important to define which patients stand to benefit and how long the treatment takes to produce favorable changes. Moreover, the magnitude of the effect needs to be re-evaluated in terms of quantifying the

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CPAP: continuous positive airway pressure; APAP: automatic positive airway pressure; BMI: body mass index; HbA1c: haemoglobin A1c.
changes in insulin sensitivity, fasting and post-prandial glucose levels and HbA1c. These issues should be addressed by large-scale, long-term, randomised controlled trials. In the authors’ opinion, the accumulating evidence for a positive effect of CPAP on glycemic control is very promising and warrants careful attention. It has recently been realised that OSAS aggravates glycemic control, even at the earliest stages of glucose intolerance \cite{15}, opening rich perspectives for application of CPAP. Patient health care is anticipated to have improved by 2020 and physicians will be able to make better and more individualised use of CPAP to affect favorable changes in glucose homeostasis, targeting both hypoxia and hyperglycemia.

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S- Editor Zhang HN  L- Editor Roemmele A  E- Editor Liu N