The Impact of Treatment of Obstructive Sleep Apnoea Syndrome on Glycaemic Control in Patients with Diabetes Mellitus

a report by

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Obesity is, typically, a common feature of both type 2 diabetes mellitus and of obstructive sleep apnoea syndrome (OSAS). Thus, it seems reasonable to be suspicious of some overlap between the two disease entities. For example, in a French study, 595 males with suspected OSAS underwent both nocturnal polysomnography and a two-hour oral glucose-tolerance test. OSAS was confirmed in 494 patients; type 2 diabetes was present in 30.1% and impaired glucose tolerance (IGT) was diagnosed in 20.0% of the patients.[1] These findings suggest a significant overlap between the two diseases, but this clinic-based sample of obese patients (body mass index (BMI) 30.6±0.2) had been selected on the basis of presentation with typical symptoms of OSAS. However, a Japanese study of OSAS patients also showed a high prevalence of diabetes or IGT: in 34 patients, 13 were diagnosed with diabetes mellitus (38.2%); 12 with a pathological glucose tolerance (35.3%); and only nine subjects had a normal response (26.5%) in an oral glucose-tolerance test.[2] These studies investigated subjects with confirmed OSAS for disturbances in glucose metabolism. It is not currently known how many patients with confirmed diabetes mellitus also suffer from OSAS, especially when they do not present with the typical symptoms of OSAS.

Obstructive Sleep Apnoea Syndrome and Insulin Resistance

A typical metabolic feature of both type 2 diabetes and OSAS is insulin resistance. The presence of increased insulin resistance has repeatedly been reported in patients with OSAS. In recent years, several investigators reported insulin resistance to be an independent feature of the OSAS apart from the role of the typical obesity of these patients.[3–5]

Some authors have speculated that, in patients with OSAS, the increased insulin resistance is at least partially mediated by increased sympathetic activity caused by frequent nocturnal micro-arousals and nocturnal hypoxaemia.[6–8] Since micro-arousals and hypoxaemia can be effectively overcome by adequate nasal continuous positive airway pressure (CPAP) therapy, a reduction of insulin resistance in OSAS patients could be expected. Given that these patients also suffer from type 2 diabetes with insulin resistance – a key feature of this condition – one could easily speculate about an improvement of glycaemic control by CPAP therapy in patients with both conditions. However, recent studies provide evidence that the insulin resistance is an independent feature of OSAS and can be improved with CPAP therapy;[5] these studies have also demonstrated that obesity was the main determinant of insulin resistance in these patients. It is still unclear whether CPAP treatment can reduce the insulin resistance to a degree necessary to improve glycaemic control in diabetic patients.

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Influence of Continuous Positive Airway Pressure Therapy on Diabetes Mellitus

To date, there have been only a few published reports on the effect of CPAP therapy in patients suffering from both type 2 diabetes mellitus and OSAS.[9–12] The parameters of these studies are presented in *Table 1*.

The first study presented on the topic demonstrated a significant increase in insulin sensitivity in a group of nine very obese patients with type 2 diabetes and OSAS after three months of CPAP treatment.[9] A strong point of the study was the use of euglycaemic hyperinsulinaemic clamp tests to determine insulin sensitivity. The study had some limitations. The patients in the study population had considerable obesity and had different antidiabetic treatment modes (insulin, oral antidiabetic drugs or diet alone) without sufficient glycaemic control. There is also a lack of information regarding changes in lifestyle during the treatment period (e.g. exercise, alcohol and nicotine consumption), concomitant diseases such as hypertension, the duration of diabetes and the absence or presence of autonomous diabetic neuropathy, which is itself a known risk factor for OSAS.[13] Unfortunately, the reported improvement of insulin sensitivity was not accompanied by an improvement in haemoglobin A1c (HbA_{1c}) levels.

Against this background, the authors' study group investigated nine subjects with well-controlled diabetes mellitus before, two days after and three months after onset of CPAP therapy with the euglycaemic hyperinsulinaemic clamp procedure.[10] The study failed to demonstrate rapid significant changes of insulin sensitivity after two nights of CPAP treatment, but, after three months of effective CPAP treatment, insulin sensitivity was significantly improved. However, there was also no improvement in the HbA_{1c} or fructosamine levels.

A 2005 control study measured interstitial glucose continuously over a period of 72 hours before and after CPAP treatment in 25 patients with type 2 diabetes and OSAS.[11] The mean one-hour postprandial (breakfast, dinner, lunch) glucose levels were significantly lower after a CPAP treatment period of 83+50 days. HbA_{1c} levels were also improved by CPAP treatment.

In this study, the adequate and regular use of CPAP therapy was very important. In patients using their CPAP device regularly and for more than four hours per night, the decrease in HbA_{1c} levels and blood-glucose values was more distinct than in the subgroup with less CPAP therapy adherence.

RESMED

Treating sleep apnea with CPAP improves Insulin Sensitivity[1]

Recent publications have shown 58% of type 2 diabetics suffer from obstructive sleep apnea (OSA)[2]. OSA occurs when the airway temporarily collapses during sleep, preventing or restricting breathing for at least ten seconds or more. These events can occur several hundred times a night, severely disrupting sleep and negatively impacting cardiovascular function.

If your patients suffer from any of the following symptoms, they may have OSA:

- **Hypertension**
- **Excessive daytime sleepiness**
- **Snoring**
- **Pauses in breathing during sleep, gasping or choking**

OSA can be effectively treated with CPAP therapy, yet most sufferers have not been diagnosed and are not aware that they may have OSA.

For a diabetic patient, treatment of OSA can:

- **Improve insulin sensitivity[1]**
- **Lower systemic blood pressure[3]**
- **Improve quality of life**
  ...and alleviate other symptoms associated with OSA

Identifying diabetic patients with OSA is now a simple process for any physician using an ApneaLink™ screener, shown below.

[1] Harsch et al. (2003) [2] Resnick et al. (2003) [3] Becker et al. (2003)

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ApneaLink™ provides data in a simple, easy to read format on critical physiological parameters including Apnea-Hypopnea Index (AHI), oxygen desaturation index (ODI), pulse oximetry, snoring events, flow limited breathing and breath rate

Table 1: Data from Studies Investigating the Effect of Continuous Positive Airway Pressure Therapy on Glycaemic Control in Diabetic Patients (Without Relevant Changes in Antidiabetic Therapy)

Author	Brooks[9]	Harsch[10]	Babu[11]	Hasaballah[12]
Number of patients[a]	9	9	24	38
Diabetes therapy (combined with diet)	OAD Insulin	OAD	OAD Insulin Insulin + OAD	OAD Insulin
BMI (kg/m^2)	42.2±4.3	37.3±5.6	42.7±8.7	42±9.5
Study duration	Four months	91.4±35.5 days	83±50 days	134±119 days
Degree of OSAS	Severe	Severe	Severe	Severe
Insulin sensitivity (Clamp)	Signs of improvement	Signs of improvement	No difference	No difference
HbA_{1c} at onset of study	8.9±1.5%	6.4±0.7%	8.3±2.2%	7.8±1.4%
HbA_{1c} at end of study	8.9±1.2%	6.3±0.6%	7.9±2.0%[b] 8.7±2.5%[c]	7.3±1.3%

a. Number of patients who completed the study; b. CPAP therapy per night >4 hours; c. CPAP therapy per night <4 hours. OAD: oral antidiabetic drugs.

Furthermore, the improvement in glycaemic control was greater in the more poorly controlled patients (i.e. higher baseline HbA_{1c} value).

A significant improvement in HbA_{1c} in severely obese patients with type 2 diabetes and severe OSAS due to CPAP therapy has also been demonstrated.[12]

To summarise, although there seems to be a tendency towards an improvement of glucose metabolism in diabetic patients the worse their glycaemic control and given not too many co-morbidities, these studies suffer from low patient numbers and sometimes very heterogeneous samples and cover a short time span.

Clinical End-points

Apart from judging the effectiveness of the treatment by surrogate parameters such as HbA_{1c}, several colleagues know from experience that it is easier to achieve stable blood glucose profiles in diabetic patients with OSAS who are effectively treated by CPAP – an observation that still requires further confirmation in studies.

From the diabetologist's point of view, there is still a requirement for research to address the effect of CPAP on glucose metabolism. There is a lack of long-term studies, since the studies addressing glucose metabolism, previously described in detail, cover only a few months.

The fate of patients with diabetes mellitus and OSAS is typically determined by cardiovascular complications.[13] Long-term studies on these 'hard' end-points in patients with both diseases are currently not available. However, clinically beneficial effects of CPAP therapy in several studies with OSAS patients – sometimes also including a few diabetic subjects – have been demonstrated, and give cause for optimism that these results may also be applicable to patients with both diseases. In OSAS patients, there is evidence that adequate CPAP therapy reduces the mean arterial blood pressure, improves the left ventricular ejection fraction and significantly decreases the risk of fatal and non-fatal cardiovascular events (in 372 patients with treated OSAS versus 235 untreated patients with severe OSAS and 403 untreated patients with mild or moderate OSAS).[14–16] Furthermore, CPAP therapy raises high-density lipoprotein cholesterol after six months of therapy.[17]

Open Questions

Another fascinating question, as yet unanswered, is whether CPAP therapy in prediabetic patients with OSAS (e.g. patients with impaired fasting glucose or pathological glucose-tolerance testing) have a risk reduction to developing overt type 2 diabetes mellitus due to CPAP therapy. A possible mechanism favouring such a hypothesis could be the improvement in insulin sensitivity observed in many studies due to CPAP therapy. Whether this degree of reduction of insulin resistance is sufficient to have preventive effects is as yet unknown.

The observations and studies mentioned in this article refer to patients with OSAS alone or with OSAS and type 2 diabetes. Although not driven by insulin resistance – but sometimes also causing sleep disturbances or sleep-disordered breathing by neuropathic complications – the possible implications of treatment of sleep-disordered breathing in type 1 diabetic patients is largely unknown.[18] ■

1. Meslier N, Gagnadoux F, Giraud P, et al., Impaired glucose-insulin metabolism in males with obstructive sleep apnoea syndrome, *Eur Respir J*, 2003;2:156–60.
2. Katsumata K, Okada T, Miyao M, Katsumata Y, High incidence of sleep apnea syndrome in a male diabetic population, *Diabetes Res Clin Pract*, 1991;13(1-2):45–51.
3. Ip MS, Lam B, Ng MMT, et al., Obstructive sleep apnea is independently associated with insulin resistance, *Am J Respir Crit Care Med*, 2002;165:670–76.
4. Punjabi NM, Sorkin JD, Karzel LI, et al., Sleep-disordered breathing and insulin resistance in middle-aged and overweight men, *Am J Respir Crit Care Med*, 2002;165:677–82.
5. Harsch IA, Pour Schahin S, Radespiel-Tröger M, et al., Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome, *Am J Respir Crit Care Med*, 2004;169:156–62.
6. Coy TV, Dimsdale JE, Ancoli IS, Clausen J, Sleep apnoea and sympathetic nervous system activity: a review, *J Sleep Res*, 1996;5:42–50.
7. Marrone O, Riccobono L, Salvaggio A, et al., Catecholamines and blood pressure in obstructive sleep apnea syndrome, *Chest*, 1993;103:722–7.
8. Hedner JA, Darpo B, Ejnell H, et al., Reduction in sympathetic activity after long-term CPAP treatment in sleep apnoea: cardiovascular implications, *Eur Respir J*, 1995;8:222–9.
9. Brooks B, Cistulli PA, Borkman M, et al., Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness, *J Clin Endocrinol Metab*, 1994;79:1681–5.
10. Harsch IA, Schahin SP, Brückner K, et al., The effect of continuous positive airway pressure treatment on insulin sensitivity in patients with obstructive sleep apnoea syndrome and type 2 diabetes, *Respiration*, 2004;71:252–9.
11. Babu AR, Herdegen J, Fogelfeld L, et al., Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea, *Arch Intern Med*, 2005;165:447–52.
12. Hassaballa HA, Tulaimat A, Herdegen JJ, Mokhlesi B, The effect of continuous positive airway pressure on glucose control in diabetic patients with severe obstructive sleep apnea, *Sleep Breath*, 2005;9:176–80.
13. Stoohs RA, Guilleminault C, Malone S, et al., Cardiovascular changes associated with obstructive sleep apnea syndrome, *Chest*, 1991;22:1021–5.
14. Pepperell JCT, Ramdassingh-Dow S, Crosthwaite N, et al., Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea. A randomized parallel trial, *Lancet*, 2001;359:204–10.
15. Yaneko Y, Floras JS, Usui K, et al., Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructice sleep apnea, *N Engl J Med*, 2003;348:1233–41.
16. Marin JM, Carrizo SJ, Vicente E, Agusti AG, Long-term cardio-vascular outcomes in men with obstructive sleep apnoea, hypop-noea with or without treatment with continuous positive airway pressure: an observational study, *Lancet*, 2005;365:1046–53.
17. Borgels J, Sanner BM, Bitlinski A, et al., Obstructive sleep apnoea and its therapy influence high-density lipoprotein cholesterol serum levels, *Eur Respir J*, 2006:27:121–7.
18. Ficker JH, Dertinger SH, Siegfried W, et al., Obstructive sleep apnoea and diabetes mellitus: the role of cardiovascular autonomic neuropathy, *Eur Respir J*, 1998;11(1):14–19.