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Obstructive sleep apnoea syndrome impairs insulin sensitivity independently of anthropometric variables

Francesco Tassone*, Fabio Lanfranco*, Laura Gianotti*, Sonia Pivetti†, Fabrizia Navone†, Ruth Rossetto*, Silvia Grottoli*, Valerio Gai†, Ezio Ghigo* and Mauro Maccario*

*Division of Endocrinology and Metabolic Diseases, Department of Internal Medicine, University of Turin and †Emergency Department-Emergency Medicine, A. S. O. San Giovanni Battista di Torino, Italy

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Summary

OBJECTIVES **Obstructive sleep apnoea syndrome (OSAS) is strongly associated with obesity and characterized by endocrine and metabolic changes including impairment of insulin sensitivity. The aim of this study was to further clarify the insulin dynamics and glucose metabolism in this condition.**

DESIGN, PATIENTS AND MEASUREMENTS **We studied 30 obese patients with OSAS [OSA, 21 males, 9 females; age, mean ± SEM: 53·1 ± 1·7 years; body mass index (BMI): 38·6 ± 1·1 kg/m^2; waist-to-hip ratio (WHR): 0·99 ± 0·07; Apnoea/Hypopnoea Index (AHI): 40·5 ± 5·8 events/h of sleep] by means of overnight polysomnography and oral glucose tolerance testing. Mathematical models were used to assess: (i) whole-body insulin sensitivity index (ISI composite); (ii) hepatic ISI; (iii) the first phase of insulin secretion ($\Delta I_{30'-0'}/\Delta G_{30'-0'}$). Results were compared with those in 27 weight-matched patients with simple obesity (OB, 12 males, 15 females; age: 48·1 ± 2·8 years, BMI: 38·5 ± 1·4 kg/m^2, WHR: 0·94 ± 0·09; AHI: 2·15 ± 0·5 events/h of sleep) and with 20 normal subjects (NS, 15 females; 5 males, age: 40·4 ± 2·9 years; BMI: 22·2 ± 0·6 kg/m^2).**

RESULTS **ISI composite value was significantly lower in OSAS (1·71 ± 1·41) than in OB (3·08 ± 0·27) and in NS (6·1 ± 0·4) even after age-, BMI- and WHR-adjustment. Similarly, hepatic ISI was significantly different among the three groups (OB = 0·25 ± 0·02, OSAS = 0·16 ± 0·014 and NS = 0·55 ± 0·04). Sex did not affect ISI indices. Insulin secretion estimates were not significantly different among the three groups.**

DISCUSSION **Obese patients with obstructive sleep apnoea syndrome are more insulin resistant than patients with simple obesity independently of the degree and distribution of adiposity. The worsening in insulin sensitivity in obstructive sleep apnoea syndrome patients could reflect the hypoxic state and would account for the increased vascular risk in this condition.**

Introduction

Obstructive sleep apnoea syndrome (OSAS) is characterized by the presence of repetitive apnoea and hypopnoea during sleep, daytime sleepiness and cardiopulmonary dysfunction (Strollo & Rogers, 1996). Epidemiological studies estimate that this condition affects 2–4% of middle-aged adults (Young *et al.*, 1993).

Obstructive sleep apnoea is often associated with obesity (particularly the android-central type) in which different abnormalities of pulmonary function may coexist. Abnormalities in chest wall mechanics, reduced respiratory compliance and impaired respiratory muscle function contribute to the pulmonary dysfunction of severely obese patients. The coexistence of hypoxaemia with obesity and hypoventilation defines the Pickwickian syndrome (Burwell *et al.*, 1956). In this context it is mandatory to differentiate central from obstructive sleep apnoea with the gold standard procedure, i.e. nocturnal polysomnography, because of both the different treatments required and the potential consequences that OSAS implies.

Simple obesity is clearly associated with coronary heart disease (CHD) and is an established marker of cardiovascular risk (Braunwald *et al.*, 2001). The distribution of body fat may also play a role in the development of CHD, with abdominal adiposity conferring a greater risk in both women and men (Braunwald *et al.*, 2001).

Obstructive sleep apnoea is an independent risk factor for hypertension (Lavie *et al.*, 2000; Peppard *et al.*, 2000) and is thought also to be a cause of premature death, ischaemic heart disease and stroke (Wright *et al.*, 1997). Furthermore, OSAS is characterized by specific worsening in endocrine and metabolic abnormalities (such as GH/IGF-I, hypothalamo–pituitary–adrenal, thyroid and gonadal axis), which can account for a further increase in cerebro- and cardiovascular risk in patients with

Correspondence: Dr M. Maccario, Divisione di Endocrinologia, Università di Torino C. so Dogliotti 14, 10126 Torino, Italy. Tel.: +39 011 6334317; Fax: +39 011 6647421; E-mail: mauromac@interfree.it

OSAS. On the other hand, visceral obesity, typically present in OSAS, could account 'per se' for these metabolic abnormalities (Bjorntorp, 1992).

Previous investigations into the role of sleep-breathing disorders in insulin sensitivity and glucose homeostasis in obesity reported conflicting data. While some authors observed that this relationship was entirely dependent on body mass (Stoohs *et al.*, 1996), others have shown that biochemical indices of insulin resistance are higher that in body mass index (BMI)-matched nonapnoeic controls (Vgontzas *et al.*, 2000).

The purpose of this study was therefore to evaluate insulin sensitivity/resistance and secretion in a sample of obese patients affected with OSAS, comparing them with nonapnoeic obese patients.

Research methods and procedures

Subjects

The subjects enrolled in this study belonged to a cohort of outpatients with obesity who reported symptoms such as daytime somnolence and nocturnal snoring, suggesting possible sleep apnoea syndrome. Exclusion criteria included unstable or uncontrolled cardiopulmonary disease, malignancies, recent surgery of the upper airways, thyroid disorders, and treated hypertension. Subjects were also excluded if already diagnosed (or receiving medical treatment) for sleep-disordered breathing.

After a polysomnographic study, the first consecutive 30 obese patients with OSAS [OSA, 21 males, 9 females; age, mean ± SEM: 53·1 ± 1·7 years; BMI: 38·6 ± 1·1 kg/m^2; waist-to-hip ratio (WHR): 0·99 ± 0·07; Apnoea/Hypopnoea Index (AHI): 40·5 ± 5·8 events/h of sleep] and the first consecutive 27 obese patients without OSAS (OB, 12 males, 15 females; age: 48·1 ± 2·8 years, BMI: 38·5 ± 1·4 kg/m^2, WHR: 0·94 ± 0·09; AHI: 2·15 ± 0·5 events/h of sleep) were recruited. All OSA women but one were postmenopausal; nine out of 15 OB women were postmenopausal; women with regular menses were studied in the early follicular phase.

All subjects gave their written informed consent to participate in the study, which had been approved by the local ethical committee.

A cohort of 20 normal subjects (NS, 15 females, 5 males, age: 40·4 ± 2·9 years; BMI: 22·2 ± 0·6 kg/m^2) recruited among the personnel of our department and their relatives, without either metabolic disorders or first-degree relatives affected by diabetes and obesity, were used to define our normality reference of glucose and insulin data from oral glucose tolerance tests (described later).

Polysomnographic procedure

All the patients underwent a standard overnight polysomnography (ATScc, 1989; AARC-APT, 1995) using a 16-channel polysomnographic recording system (Compumedics Sleep Pty Ltd, Abbotsford, Australia), which included the following standard parameters: electroencephalogram; electro-oculogram; electromyogram; continuous nasal airflow by stalk-mounted thermocouples; body position; thoracic and abdominal respiratory efforts (recorded by respiratory inductive plethysmography using a mercury strain gauge); heart rate and rhythm by electrocardiography; oxyhaemoglobin saturation (SaO_2) by pulse oximetry.

The nocturnal polysomnographic recordings were scored using 30-s epochs following the criteria of Rechtschaffen and Kales (1968) for sleep/wake determination and sleep staging.

Apnoea was defined as cessation of airflow for at least 10 s. A reduction in the amplitude of the ribcage and abdominal excursions with a decrease in ventilation exceeding 50% that lasted at least 10 s associated with an SaO_2 reduction of at least 4% was defined as hypopnoea. According to Lindberg *et al.* (1999), OSAS was arbitrarily defined as more than five episodes of apnoea or hypopnoea per hour of sleep; the AHI was defined as the average number of episodes of apnoea and hypopnoea per hour of sleep.

Endocrino-metabolic assays

The day after the polysomnographic recording, all patients underwent an oral glucose tolerance test (OGTT) with assays for both insulin and glucose levels at 0, 30, 60, 90 and 120 min. The OGTT began in the morning at 0830–0900 h after an overnight fast and 30 min after an indwelling catheter had been placed into an antecubital vein of the forearm and kept patent by slow infusion of isotonic saline. Blood samples were drawn basally and then every 30 min from 0 up to 120 min. Serum glucose and insulin levels were measured at each time point.

Serum insulin levels (expressed as pmol/l) were measured in duplicate by immunoradiometric assay (INSIK-5, Sorin, Saluggia, Italy). The sensitivity of the assay was 27·8 pmol/l. The inter- and intra-assay coefficients of variation were 6·2–10·8% and 5·5–10·6%, respectively.

Plasma glucose (expressed as mmol/l) was determined by the glucose oxidase colorimetric method (GLUCOFIX; Menarini Diagnostics, Firenze, Italy).

The insulin sensitivity/resistance estimate was computed according to the formulae developed by Matsuda and DeFronzo (1999). This index incorporates insulin and glucose levels when fasting and during the OGTT, giving a 'composite' estimate of whole-body insulin sensitivity (the so-called ISI composite) strongly associated with clamp-measured total glucose disposal in subjects with various degrees of glucose tolerance and insulin sensitivity (Matsuda & DeFronzo, 1999). The same authors proposed a hepatic Insulin Sensitivity Index (ISI) [k/(fasting plasma glucose × fasting plasma insulin)], which closely agrees with that measured directly with tritiated glucose (Matsuda & DeFronzo,

1999). The first phase of insulin secretion was measured as the ratio of the 30-min increase in insulin concentration to the 30-min increase in glucose concentration following the OGTT ($\Delta I_{30'-0'}/\Delta G_{30'-0'}$). This index has been demonstrated to be a good surrogate for intravenous glucose tolerance test-measured first-phase of insulin secretion (Phillips *et al.*, 1994).

Statistical analysis

Data are expressed as mean (± SEM) of absolute values.

The statistical analysis was performed by a multiple analysis of variance (MANOVA) considering:

- condition of subjects (normal, simple obese, obese with OSAS) and gender as independent factors;
- (i) ISI composite values; (ii) hepatic ISI; (iii) the ratio of the 30-min increase in insulin concentration to the 30-min increase in glucose concentration following the OGTT, as dependent variables;
- age, BMI and WHR as covariates.

The Neuman–Keuls test was used for posthoc analysis and simple linear correlation (Pearson r) was used, where appropriate.

Results

Clinical and polysomnographic sleep data are shown in Table 1.

Simple obese patients were not significantly different from OSA patients in terms of age, BMI, WHR; there were obvious significant differences in terms of respiratory variables during sleep. However, the total sleep time and the sleep efficiency were similar during the polysomnographic recording.

OSA patients showed increased glucose and insulin responses to oral glucose challenge compared to OB (Fig. 1). Glucose and insulin levels 120 min after the OGTT were higher in OSA than in OB patients (8·37 ± 0·57 *vs.* 7·51 ± 0·63 mmol/l and 991·4 ± 105·9 *vs.* 591·6 ± 67·5 pmol/l, respectively, $P < 0·02$). Five OSA and three OB patients proved to be diabetic; 10 OSA and five OB patients had impaired glucose tolerance (IGT).

Table 1 Clinical and polysomnographic data of the obese patients (OB) and patients with obstructive sleep apnoea syndrome (OSAS)

	OSAS	OB	*P*-value
n	30	27	
Male/Female	21/9	12/15	
Age (years)	53·1 ± 1·7	48·1 ± 2·8	ns
BMI (kg/m^2)	38·6 ± 1·1	38·5 ± 1·4	ns
Waist-to-hip ratio	0·99 ± 0·07	0·94 ± 0·09	ns
Haematocrit	43·5 ± 0·9	41·3 ± 0·6	ns
Mean SaO_2 (%)	87·9 ± 1·6	94·1 ± 1·0	< 0·05
Nadir SaO_2 (%)	72·1 ± 2·8	83·9 ± 2·2	< 0·05
Sleep efficiency (%)	46·5 ± 6·0	44·9 ± 4·7	ns
Total sleep time (min)	281·4 ± 37·6	285·5 ± 26·8	ns
Non-REM sleep time (%)	95·8 ± 2·2	97·0 ± 1·6	ns
REM sleep time (%)	4·2 ± 2·2	3·0 ± 1·7	ns
AHI (events/h)	40·5 ± 5·8	3·3 ± 1·3	< 0·05

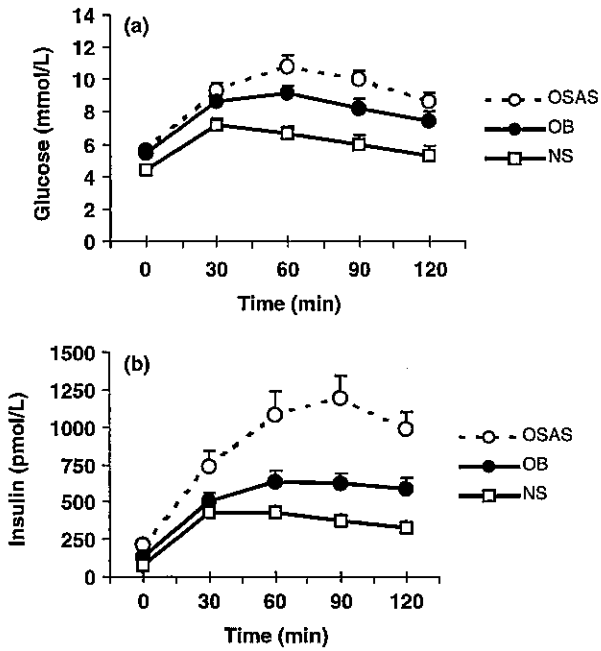

Fig. 1 Glucose and insulin levels in normal subjects (NS), obese patients (OB) and obese patients with obstructive sleep apnoea syndrome (OSAS) during OGTT.

Whole-body ISI composite values sharply differentiated ($P < 0·0001$) OB (3·08 ± 0·27) and OSA (1·71 ± 1·41) from NS (6·1 ± 0·4) even after age-, BMI- and WHR-adjustment (adjusted means, OB *vs.* OSA *vs.* NS: 3·32 *vs.* 1·94 *vs.* 5·57, respectively), suggesting that OSA patients were more insulin resistant than OB ($P < 0·01$) independently from age, BMI and WHR (Fig. 2). Similarly, hepatic ISI was significantly different among the three groups (OB = 0·25 ± 0·02, OSA = 0·16 ± 0·014 and NS = 0·55 ± 0·04) after age-, BMI- and WHR-adjustments (adjusted means, OB *vs.* OSA *vs.* NS: 0·29 *vs.* 0·20 *vs.* 0·47, respectively, $P < 0·005$) (Fig. 2).

Insulin secretion estimates were similar in OB (137·8 ± 21·7 pmol/mmol) and OSA (139·2 ± 18·7 pmol/mmol), both being lower than NS (256·2 ± 54·0 pmol/mmol; $P < 0·05$). After adjustment for age, BMI and WHR this difference disappeared. No significant correlation of ISI composite, hepatic ISI and $\Delta I_{30'-0'}/\Delta G_{30'-0'}$ with haematocrit, SaO_2, oxygen partial pressure (PO_2) and carbon dioxide partial pressure (PCO_2) was found.

The interaction between either sensitivity indices or insulin secretion index and gender in a MANOVA model of analysis was not significant ($F = 0·58$ and $P = 0·56$; $F = 0·07$ and $P = 0·93$; $F = 1·25$ and $P = 0·29$, respectively, for ISI composite, hepatic ISI and $\Delta I_{30'-0'}/\Delta G_{30'-0'}$).

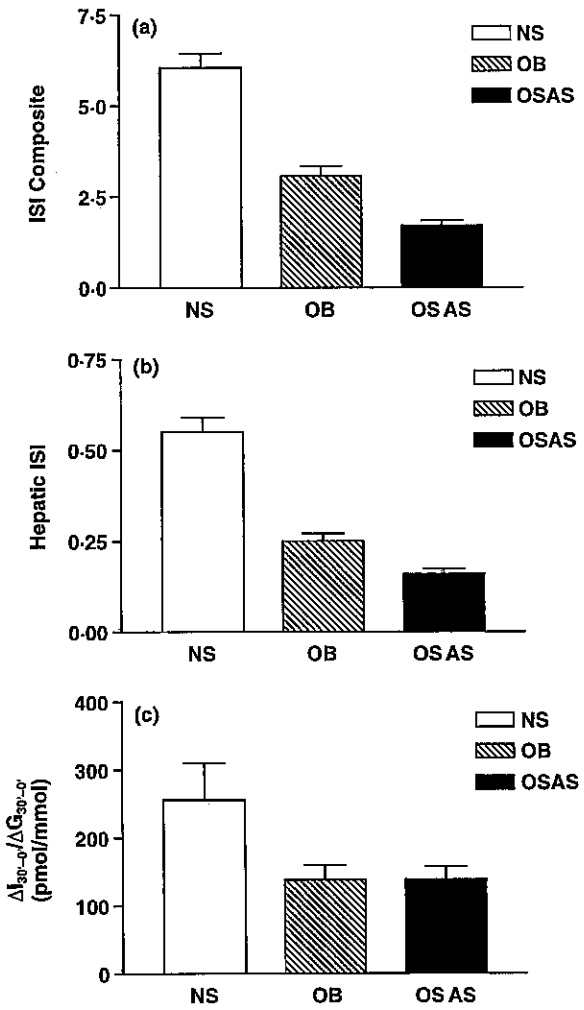

Fig. 2 ISI composite, hepatic ISI and $\Delta I_{30'-0'}/\Delta G_{30'-0'}$ in normal subjects (NS), obese patients (OB) and obese patients with obstructive sleep apnoea syndrome (OSAS).

Discussion

This study shows that obese patients with obstructive sleep apnoea are more insulin resistant than patients with simple obesity, being specifically impaired in terms of hepatic insulin sensitivity. The lower insulin sensitivity in the OSA group is observed despite a nonsignificant difference in the first phase of insulin secretion capacity and also independently of the amount and distribution of fat. Even if we have not used the gold standard test to assess insulin sensitivity in humans, that is the euglycaemic–hyperinsulinaemic clamp (DeFronzo *et al.*, 1979; Fulcher *et al.*, 1992), the insulin sensitivity index obtained from oral glucose tolerance testing has been reported to be closely correlated with clamp studies (Matsuda & DeFronzo, 1999). The same remarks apply to the measure used as surrogate for the first phase of insulin secretion (Phillips *et al.*, 1994). Furthermore, we have not found any association between our indices of insulin sensitivity/resistance and respiratory parameters, in contrast to Tiihonen *et al.* (1993) who reported that insulin resistance is related to the severity of sleep apnoea.

Obstructive sleep apnoea is common in obese patients. It is an established independent risk factor for hypertension (Lavie *et al.*, 2000; Peppard *et al.*, 2000) and is also thought to be a cause of premature death, ischaemic heart disease and stroke (Wright *et al.*, 1997). Moreover, the severity of obstructive sleep apnoea syndrome is positively associated with waist-to-hip ratio (Lavie *et al.*, 2000) and visceral obesity is one of the features of the insulin resistance (or metabolic) syndrome that is associated with increased risk of cardiovascular diseases (Bjorntorp, 1992).

Investigations into the role of sleep-breathing disorders on insulin dynamics and glucose metabolism in obese individuals reported conflicting data. In fact, while some authors found that this relationship was entirely dependent on body mass (Stoohs *et al.*, 1996), others have reported that biochemical indices of insulin resistance are higher than in BMI-matched nonapnoeic controls (Vgontzas *et al.*, 2000). Consistent with the latter finding, in the present study we observed that insulin resistance is greater in OSA patients than in simple obesity even after adjusting for confounding variables such as BMI and WHR. Several hypotheses could be taken into consideration to explain these results. Data on *in vitro and in vivo* animal studies reported that hypoxia could lead to a decreased insulin secretion (Dionne *et al.*, 1993), possibly through a decrease in adenosine triphosphate (ATP) production in the beta cell (Narimiya *et al.*, 1982). Furthermore, animal studies reported other possible mechanisms underlying insulin resistance during hypoxia, such as reduced insulin receptor responsiveness and reduced insulin receptor tyrosine kinase activity (Cheng *et al.*, 1997).

In humans, the effect of hypoxia on glucose homeostasis has been investigated in subjects exposed to altitude. In this model an increase in hepatic glucose output coupled with reduced whole-body insulin-stimulated glucose uptake has been observed (Larsen *et al.*, 1997). Interestingly, these hypoxic subjects shared with human obese subjects with OSAS multiple alterations in endocrine pathways (involved in decreasing insulin sensitivity), such as augmented catecholamine levels (Strollo & Rogers, 1996) and increased hypothalamo–pituitary–adrenal drive (Bratel *et al.*, 1999).

Moreover, in the study by Vgontzas *et al.* (2000), hypercytokinaemia (TNFα and IL-6) was reported to play a possible role in the metabolic disturbances of visceral obesity associated with sleep apnoea but this was not the case for leptin levels.

In addition, obese patients with OSAS show a more severe impairment of somatotroph function than those with simple obesity (Gianotti *et al.*, 2002). As it is well known that adult patients

with GH deficiency are characterized by insulin resistance (Johansson *et al.*, 1995) and share features of the so-called 'metabolic-' or 'X-' syndrome (Hew *et al.*, 1998), somatotroph insufficiency could also account for the present findings on glucose homeostasis. Our data agree with recent studies (Fuyuno *et al.*, 1999; Vgontzas *et al.*, 2000; Ip *et al.*, 2002) in which only fasting insulin levels or homeostasis model assesment-insulin resistance (HOMA-IR) values were used as surrogate estimates of insulin resistance, and with those by Punjabi *et al.* (2002) that were based on a (larger) group of only male subjects. Conversely, a study performed with simultaneous intravenous infusion of somatostatin, glucose and insulin reported an insulin-resistant state in sleep-disordered breathing entirely dependent on body mass (Stoohs *et al.*, 1996).

Although it has been reported that premenopausal women are more insulin sensitive than men (Ruderman *et al.*, 1998), in our study the gender of patients did not affect either insulin sensitivity or secretion in line with the results of Ip *et al.* (2002) and with the most extensive work of the European Group for the study of Insulin Resistance (Ferrannini *et al.*, 1997).

In conclusion, obese patients with obstructive sleep apnoea are more insulin resistant than patients with simple obesity. Thus, obstructive sleep apnoea syndrome further impairs insulin sensitivity in obesity, independently of the degree and distribution of adiposity. The worsening in insulin sensitivity in obstructive sleep apnoea syndrome patients could reflect the hypoxic state and would account for the increased vascular risk in this condition.

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