

UNIVERSITA' DEGLI STUDI DI CATANIA
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Coordinatore: Prof. Carlo Vancheri

Dr. Raffaele Campisi

**INSULINE RESISTANCE AND INSULINE
SENSIBILITY IN PATIENTS WITH OBSTRUCTIVE
SLEEP APNEA**

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Tutor: Chiar.mo Prof. Giuseppe Di Maria

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Background

Obstructive sleep apnea (OSA), also referred to as obstructive sleep apnea-hypopnea (OSAH), is a sleep disorder that involves cessation or significant decrease in airflow in the presence of breathing effort. It is the most common type of sleep disordered breathing (SDB) and is characterized by recurrent episodes of upper airway collapse during sleep. These episodes are associated with recurrent oxyhemoglobin desaturations and arousals from sleep. Despite being a common disease, OSAS is underrecognized by most primary care physicians; an estimated 80% of Americans with OSAS are not diagnosed. Apnea may occur hundreds of times nightly, 1-2 times per minute, in patients with severe OSA, and it is often accompanied by wide swings in heart rate, a precipitous decrease in oxygen saturation, and brief electroencephalographic (EEG) arousals concomitant with loud breathing sounds as a bolus of air is exhaled when the airway reopens. The cardinal symptoms of sleep apnea include the "3 S's": *S*nores, *S*leepiness, and *S*ignificant-other report of sleep apnea episodes.

Recent studies suggest that OSA increases the risk of developing insulin resistance and type 2 diabetes. The aim of the present study was to assess whether obstructive

sleep apnea is a risk factor for insulin resistance, using surrogate estimates of insulin-mediated glucose uptake. We studied a population of 174 (122 males) subjects evaluated in our Sleep Lab for the suspect of OSA. All subjects underwent a standard nocturnal polysomnography (Compumedics S-Series). The HOMA index, an index of insulin resistance and the QUICKI index, an index of insulin sensitivity, were calculated from the values of fasting glucose and insulin obtained in the morning.

The percentage of patients with iper-triglyceridemia was significantly higher in patients with OSAS than in controls ($P < 0.05$). Insulin resistance ($\text{HOMA} > 2.4$) was higher in OSAS patients than in controls ($P < 0.05$), as well as BMI values were higher in patients with OSAS than in controls ($P < 0.05$).

The results showed that the risk factors for insulin resistance ($\text{HOMA} > 2.45$) were predominantly the BMI ($\text{OR } 2.4$, 95 % CI 1.3-4.6, $P < 0.001$), OSA ($\text{OR } 4.0$, 95 % CI 1.6 -9.7, $P < 0.001$) and hypertension ($\text{OR } 2.3$, 95% CI 1.2-4.3, $P < 0.001$).

Revealed no correlation with sex, age, hypercholesterolemia and ipertrigliceridemia.

We did a multiple regression in which the OSAS ($\text{OR } 2.7$, 95 % CI 1.2-3.70, $P < 0.05$) and BMI ($\text{OR } 2.3$, 95% CI 0.29-2.70, $P < 0.05$), but not hypertension ($\text{OR } 1.8$, 95% CI 0.8-6.0, $P < 0.8$) were independent risk factors for insulin resistance. From the

correlation between insulin levels and OSAS we got a positive relationship between insulin and AHI ($r = 0.32$, $P < 0.001$) and insulin levels and BMI ($r = 0.43$, $P < 0.001$).

Introduction

Sleep-disordered breathing (SDB) refers to momentary, often cyclical, cessations in breathing rhythm (apneas) or momentary or sustained reductions in the breath amplitude (hypopneas), sufficient to cause significant arterial hypoxemia and hypercapnia. These apneas and hypopneas are specific to the sleeping state and are accompanied by 1) a compromised, often even completely closed, extrathoracic upper airway (“obstructive” event); 2) a marked reduction or cessation of brain stem respiratory motor output (“central” event); and 3) a combination of central and obstructive events [1 , 2 , 3]. These ventilatory inadequacies and their accompanying intermittent hypoxemia often lead to transient arousals from sleep and sleep state fragmentation throughout the night and cause overcompensatory responses of the autonomic nervous system. This phenomenon is now known to occur with varying degrees of severity in literally millions of people throughout the world. [1]

Definition and Epidemiology

SDB represents a growing health concern. Sleep apnea has been known for centuries and was rediscovered at the beginning of the 20th century. In the late 1990s, however, different types of SDB have been recognised, with specific consequences and morbidities. At the end of the 1990s, a revised classification was suggested by the American Academy of Sleep Medicine [2] and further confirmed through the International Classification of Sleep Disorders, second edition (ICDS-2) [3], published in 2005.

There are three major SDB types with respect to prevalence and health consequences, i.e. obstructive sleep apnea syndrome (OSA), Cheyne–Stokes respiration (CSR) and central sleep apnoea (CSA) in chronic heart failure (CHF), and obesity hypoventilation syndrome (OHS). In all these conditions, hypoxia appears to affect body functioning in different ways, with specific mechanisms. Moreover, experimental models have been developed that permit a better understanding of the molecular and cellular mechanisms in response to SBD-related hypoxia. [4]

OSAS is defined by symptoms such as excessive daytime sleepiness (EDS) and daytime functioning impairment, with >5 obstructive events in one hour occurring during sleep. The scoring of ventilatory events includes apneas, hypopneas and also

episodes of increased upper airway resistance. Both the ICSD-2 [3] and American Academy of Sleep Medicine [2] guidelines recommend that this latter type of event should be included in OSAS, since the specificity of upper airway resistance syndrome [5] has not been considered, until now, to be supported by sufficient epidemiological, pathophysiological and clinical data.

Obstructive apneas are defined as a complete cessation of airflow, in the presence of rib cage and abdomen motion for at least 10 seconds, whereas hypopneas were defined as a 50% decrease of airflow, respectively, for at least 10 seconds accompanied either by a decrease in oxyhemoglobin saturation $\% \geq 4\%$ or an arousal. Central apneas were defined as the cessation of airflow and respiratory effort for at least 10 sec. Mixed apnoeas were defined as initial central apnoea followed by obstructive apnoea. [2 , 3] AHI was defined as the number of apneas-hypopneas per hour of total sleep time. The diagnosis of CSA is made when more than 50% of apnoeic events are central [3].

The prevalence of the disease is very high, ranging 5–15%, increasing linearly up to the age of 60 yrs and becoming more variable above this threshold age, at least regarding obstructive events [6]. Obstructive sleep apnea is particularly frequent in the age group between 40 and 50 years and affects mainly men (male to female ratio

2:1) obese and heavy snorers. Women are particularly affected by this syndrome after menopause , when there is not the protective action of certain hormones . In fact, data on the incidence and prevalence of syndrome depends on the criteria used to define it. The most important study conducted in the United States on a random sample aged between 30 and 60 years , showed an apnea- hypopnea index equal to or greater than 5 \rightarrow 9% of women and 24% of men [7, 8] . In the same sample, 2% of women and 4% of men , as well as presenting an apnea-hypopnea index greater than 5, complained of daytime sleepiness. Although all subjects with OSAS are snoring, not all snorers develop OSAS: the syndrome affects approximately 25 % of snorers . In the adult, the most important risk factors , in addition to snoring , are obesity and the reduction of the caliber of the upper airway.

Among children the incidence of the syndrome is between 1% and 3% and is usually associated with the presence of tonsillar hypertrophy [7].

Regarding OSA morbidity [9], there is now substantial evidence that there is a causal relationship between OSA and excessive daytime sleepiness, with cognitive impairment, including increased risk of traffic accidents [10, 11], and cardiovascular morbidity and mortality [11, 12, 13]. The cardiovascular consequences, occurrence of atherosclerosis without significant classical cardiovascular risks in OSA, seem to

appear early in the disease [14, 15].

This supports the need for early diagnosis and treatment, especially since the mortality rate is maximal in males aged 50 yrs and thereafter declines with age [4,16].

Pathophysiology and Risk factors

Conceptually, the upper airways is a compliant tube and, therefore, is subject to collapse. OSA is caused by soft tissue collapse in the pharynx. Transmural pressure is the difference between intraluminal pressure and the surrounding tissue pressure. If transmural pressure decreases, the cross-sectional area of the pharynx decreases. If this pressure passes a critical point, pharyngeal closing pressure is reached.

Exceeding pharyngeal critical pressure (P_{crit}) causes a tissues collapsing inward. The airway is obstructed. Until forces change transmural pressure to a net tissue force that is less than P_{crit} , the airway remains obstructed. OSA duration is equal to the time that P_{crit} is exceeded. Most patients with OSA demonstrate upper airway obstruction at either the level of the soft palate (ie, nasopharynx) or the level of the tongue (ie, oropharynx). Research indicates that both anatomic and neuromuscular factors are important. Anatomic factors (enlarged tonsils, volume of the tongue, soft tissue, or lateral pharyngeal walls, length of the soft palate, abnormal positioning of the maxilla and mandible), may each contribute to a decrease in the cross-sectional area of the upper airway and/or increase the pressure surrounding the airway, predisposing the airway to collapse. Note that in adults, it is very rare for enlarged tonsils and

adenoids to be a cause of OSA. Therefore, any anatomical alteration that produces or contributes to the narrowing of the upper airway promotes the collapse overnight. [1, 17] Removing the enlarged adenoids and tonsils alone rarely is an effective surgical remedy; in children, about 80% who have OSA are cured with the removal of enlarged adenoids and tonsils. There is often a misconception that enlarged adenoids and tonsils may be a singular cause of OSA in both children and adults, but this is not true.

Static and dynamic pathophysiologic factors

Both static factors and dynamic factors are involved in the development of OSA.

Static factors include surface adhesive forces, neck and jaw posture, tracheal tug, and gravity. The headquarters of the occlusion is the pharynx (in most cases the oropharynx), which represents the stretch more collapsible airway. It is known that during night the upper airways become more susceptible to collapse following hypotonia of the muscles (dilator and adductor of the pharynx) that maintain patency during wakefulness. [1] In susceptible people if the negative pressure of the upper airway during inspiration becomes greater than the force of these dilator muscles occurs the airway collapse. Any anatomic feature that decreases the size of the pharynx (eg, retrognathia) increases the likelihood of OSA. Gravitational forces are

felt simply by tilting one's head back to where the retroposition of the tongue and soft palate reduce the pharyngeal space. For most patients, OSA worsens in the supine sleeping position. An important static factor that has been found is the reduced diameter of the pharyngeal airway in wakefulness in OSA patients compared with non-OSA patients. In the absence of craniofacial abnormalities, the soft palate, tongue, parapharyngeal fat pads, and lateral pharyngeal walls are enlarged in OSA patients versus non-OSA patients. Dynamic factors include nasal and pharyngeal airway resistance, the Bernoulli effect, and dynamic adherence. The Bernoulli effect plays an important dynamic role in OSA pathophysiology. In accordance with this effect, airflow velocity increases at the site of stricture in the airway. As airway velocity increases, pressure on the lateral wall decreases. If the transmural closing pressure is reached, the airway collapses. The Bernoulli effect is exaggerated in areas where the airway is most compliant. Loads on the pharyngeal walls increase adherence and, hence, increase the likelihood of collapse. This effect helps to partially explain why obese patients, and particularly those with fat deposition in the neck, are most likely to have OSA. Moreover, the cross-sectional area of the airway in patients with OSA is smaller than that of people without OSA; this difference is due to the volume of the soft tissue, including the tongue, lateral pharyngeal walls,

soft palate, and parapharyngeal fat pads. In one study, the increased volume of these areas was independent of sex, age, ethnicity, craniofacial size, and fat deposition surrounding the UA. Given these principles, it is understandable why the likelihood of OSA is increased among obese patients, why weight loss decreases the risk of OSA, and why physical examination helps in predicting the presence of OSA. The most common risk factors include, therefore, tonsillar hypertrophy , anatomical malformations of the jaw and pharynx (including the enlargement of the tongue associated with conditions such as Down syndrome), disorders associated with the deposition of material at the level of the structures of the respiratory upper airway and malignancies. Other causes include pharyngeal edema, hypertrophy of lymphoid tissue, reduced contractility of the pharyngeal muscles secondary to neuromuscular disease and impaired coordination of respiratory muscles during inspiration, secondary to neurological diseases or degenerative diseases of the brain stem. Other factors which contribute to sleep apnea , but it can not be considered triggers are medications (antidepressants and benzodiazepines) and alcohol for their inhibitory effect on the respiratory centers. However, the clinical situation is complex because of the interplay of known static and dynamic factors and because of unknown factors. Data do not explain why sex, age, and ethnicity are not evenly distributed across

epidemiologic studies of OSA patients. Furthermore, data or physical findings are not helpful for determining with precision who will or will not have OSA and who can or who cannot be cured with upper airways surgery.

In conclusion, obesity represents the most frequent risk factor. [18] It may predispose to OSA by accumulation of fat around the neck, resulting in increased extraluminal pressure and a propensity to upper airway collapse which can sometimes be seen on flow-volume loops . [19] Fat distribution may affect the geometry of the airway, again making collapse more likely. Neck circumference is the anthropometric measurement most closely associated with OSAS, even in those with a normal BMI. [20] Increasing levels of abdominal obesity cause decreases in lung volumes which may cause a reduction in longitudinal traction predisposing to upper airway collapse. Obesity also reduces chest wall compliance and increases whole body oxygen demand, again predisposing to OSAS [21].

Anthropometric obesity indexes such as BMI, waist and neck circumference enlargement are considered as significant risk factors for OSAS development as demonstrated in a recent study of a cohort of people (both men and women) with an $AHI \geq 5$. [22]

Clinic and diagnosis of obstructive sleep apnea

The most frequent symptoms of OSA are snoring , excessive daytime sleepiness and episodes of apnea, sometimes felt by the patient but most of the times reported by the partners. Snoring in most cases it is extremely noisy, so as to disturb the partner and other family members (sometimes even the neighbors!) . In a minority of cases , however, patients report a mild snoring that will not even be noticed by the partner/partner in bed. Other symptoms that may occur during sleep are restlessness and involuntary movements , excessive sweating, waking up with choking sensation , heartburn and laryngospasm (secondary to esophageal reflux) , nocturia (very common) and , more rarely, enuresis . The most frequent symptom during daylight hours is drowsiness , which can be particularly intense and often debilitating . In a first step drowsiness occurs only when the patient is in particularly boring or when the patient relaxes, especially after meals. With the worsening of the patient's illness, rather than sleepiness, numbness becomes increasingly important and widespread. Obviously, the most catastrophic consequence of daytime sleepiness is falling asleep at the wheel, so these patients may be responsible for a large number of road accidents. [23] Sleepiness in patients with OSAS is due to the fact that nighttime sleep is not refreshing (even though most patients report that they sleep deeply)

because interrupted by continuous micro-arousal that are not felt by the patient (detectable only with the EEG). Micro-arousals usually occur at the end of each apneic episode and therefore hundreds of times during the night . Other typical symptoms are morning headaches and difficult to get up from the bed. Some patients report to be dazed, confused or disoriented and to have difficulty at the work or other tasks of daily living. [24, 25] In more severe forms may be present mood disorders such as irritability and/or depression , difficulty in social life, and neurocognitive disorders. In men it is particularly frequent impotence or decreased libido. In more severe neurocognitive disorders may be present difficulty of concentration and frequent forgetfulness. If the history of these patients is particularly striking for the presence of OSAS (is now collected by standard questionnaires) examinations did not reveal any particular sign than the presence of obesity and often neck circumference greater than 40 cm . Oropharynx examination may reveal elongated soft palate and uvula, edema and erythema of peritonsillar pillars, uvula, soft palate or posterior oropharynx, hypertrophy of the pharyngeal mucosa, enlarged tongue and tonsils. Often there is edema of the nasal mucosa (for example allergic rhinitis) which can compromise the patency of the nose and determinate nasal obstruction and contribute to oral breathing typical of the syndrome.

The gold standard for making the diagnosis of OSA is polysomnography, performed in a specialized laboratory for the study of sleep disorders. The examination involves the continuous recording during the night of the following signals :

electroencephalogram , electrooculogram and electromyogram for the evaluation of sleep stages; airflow , thoraco- abdominal movements , SaO₂, snoring, body position and electrocardiogram . In some cases it can also be recorded CO₂ and blood pressure. Approaches more simple and less expensive systems involve the use of recording systems outpatient, with a reduced number of channels, used in different combinations. The advantage of such recordings, which however never include sleep staging, consists in the fact that they can be made at the patient's home and then in a more familiar environment. The assessment of sleepiness can be done through the "multiple sleep latency test" which consists of several EEG recording to evaluate the latency of sleep during daylight hours. More simply, and most commonly, the sleepiness is evaluated through the Epworth scale, that is a questionnaire in which are described different situations in which the patient should be "at risk" of falling asleep. For every patient's response is assigned a score: the highest score showed a greater severity of sleepiness. The differential diagnosis must be made with different clinical conditions that can cause similar symptoms. In particular, daytime sleepiness

may be present in certain neurological disorders such as narcolepsy, idiopathic hypersomnia , atypical depression , and periodic leg movements in various metabolic diseases .

Treatment

The goal of treatment is to maintain the upper airway patency during sleep and prevent the occurrence of apneas . The treatment of choice is the continuous positive airway pressure (CPAP) by nasal mask during the night. It is currently regarded as the first line therapy for OSAS. The principal indication for CPAP treatment is daytime sleepiness. CPAP improves daytime sleepiness dramatically in severe cases and the effect is objectively measurable with the multiple sleep latency test (MSLT). It is noteworthy that CPAP also improves symptoms, subjective daytime sleepiness, quality of life and driving ability already in patients with mild sleep apnea with an apnea/hypopnea index (AHI) between 5 and 15 per hour of sleep during overnight polysomnography. [26, 27]

This type of ventilation was effective in 80 to 90% of patients and has been used successfully in infants and children. [28, 29] This type of treatment significantly reduces the number of apneas, improves the level of alertness and the efficiency at

work. In some patients was also documented an improvement in cognitive function , a reduction in depressive symptoms and sexual dysfunction [26, 30, 31].

These benefits are also observed in severe cases, but they disappear as soon as the treatment is stopped even if only for one night. The level of positive pressure to be applied varies from patient to patient (usually it is the greater in severe conditions).

To determine the optimal level of pressure is carried out a polysomnographic study in course of ventilation (titration). In fact the application of too low a pressure may be ineffective while a too high pressure may not be well tolerated by the patient and determine the occurrence of central apneas during sleep. In patients with cardiorespiratory diseases suboptimal pressure may cause arrhythmias or hypoventilation . [32]

CPAP have not serious side effects and patient compliance is the only real problem with this type of treatment. [33] The number of patients who regularly use CPAP is less than the number of patients who benefit from it .[34] In a study, using the internal timers, the effective use of CPAP showed a real use of the device for about two thirds of the night, for an average of 5 hours per night (35, 36). In general, patients who observe an improvement of the symptoms are those that tend to use the CPAP with greater regularity . The lack of treatment compliance may be due to side

effects such as nasal congestion and dryness or irritation of the skin or eyes (caused by air leakage from the mask). To avoid these effects and improve patient compliance interfaces available today are very sophisticated. Today, as an alternative to CPAP are available auto-CPAP that automatically adapt moment by moment, the positive pressure to the patient's needs. In patients that needs to use very high pressures or in patients with " overlap syndrome ", defined by concurrent existence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea, is often used mode Bi -PAP (two levels of positive pressure) [37, 38, 39].

Surgical procedures

Tracheostomy, effective in all cases of OSAS, was once the only treatment available, but is rarely used today. Tonsillectomy and adenoidectomy are effective in many cases during childhood whereas in adults these interventions are rarely effective. For about a decade, in adults uvulo- palatal pharyngoplasty has been the most important surgical intervention in patients with OSA, which involves the removal of the uvula , portions of the soft palate and pharyngeal tissue. This type of intervention is probably the most frequently used surgical approach in the treatment of the syndrome. The uvulo- palatal pharyngoplasty is unfortunately effective only in 40-50 % of patients and this depends on the fact that in many patients the obstruction is not linked to collapsing of the palate but is due to the base of tongue against the posterior wall of the pharynx (the glossectomy is performed in some cases to reduce the size of tongue with a large base) or the obstruction often occurs at the level of the hypopharynx.

[40] More recently the uvulo - palatal pharyngoplasty is carried out by laser . This new surgical technique is effective in about one-third (27%) of patients with obstructive sleep apnea mild or moderate. In presence of craniofacial bone changes can be performed interventions of maxillary and mandibular osteotomy . To advance the base of the tongue is used an intervention to have the 'suspension' of the hyoid .

To correct nasal obstruction, septoplasty and turbinectomy can be performed, but it is important to note that very rarely nasal obstruction alone may give rise to a syndrome of sleep apnea.

In patients with mild OSA (AHI <20 without daytime sleepiness) may be useful weight loss. Although only 5% of obese patients can lose weight and maintain the new weight over time. Dietary treatment should be recommended for all obese patients with OSAS . Unfortunately, in literature there are few data on the effectiveness of weight loss. After weight loss in many patients the clinical situation improves significantly whereas others continue to have symptoms such as excessive daytime sleepiness and snoring.

These systems can be tailored to the individual patient, are often effective in cases of mild to intermediate severity of OSA, and are often preferred to CPAP.

Insuline Resistance and Obstructive Sleep Apnea

Insulin resistance is a central part of the metabolic syndrome, a condition that is reaching epidemic proportions in Western Society and now emerging in developing countries. [41] The metabolic syndrome has many features in common with OSA including obesity, hyperlipidemia, hypertension, glucose intolerance and insulin resistance. OSA is so interwoven in the fabric of the metabolic syndrome, or Syndrome X, that the combination of OSA and metabolic syndrome has been labeled “Syndrome Z”. [42] OSA is also associated with increased cardiovascular and cerebrovascular morbidity. Recent epidemiological studies provide strong evidence that OSA itself confers independent risks for the development of hypertension. Consequently, the relationship between OSA and the multiple aspects of the metabolic syndrome and in particular with insulin resistance, are difficult to disentangle [1 , 43]. It is well known that obesity is frequently associated with OSA. Excess weight in adults is clearly associated with increased incidence of type-2 diabetes and impaired glucose tolerance (IGT). A high prevalence of type-2 diabetes and IGT may therefore be expected in patients with OSAS who are usually overweight and >40 yrs of age. [44] Adipose tissue is a central player in metabolic regulation through the production and release of multiple adipokines [45]. Moreover,

adipocytes and inflammatory cells, such as macrophages, show a high degree of interaction in obesity. The resulting picture is complex and, at present, incomplete. Recent research has explored new directions, such as the pathophysiology of different fat depots in the body, the role of hypoxia, and the interactions between adipose tissue and the central nervous system in response to nutrient excess. Obesity has also been related to chronic sleep loss, typical of the current lifestyle in both adults and children [46, 47]. Obesity is a well-established predictor of SDB. Clinical observations and population studies throughout the United States, Europe, Asia, and Australia have consistently shown a graded increase in the prevalence of SDB as body mass index, neck girth, or other measures of body habitus increases. Clinical studies of weight loss and longitudinal population studies provide strong support for a causal association. [48] Changes in body weight are known to affect OSA severity [49]. Most adult patients with OSA have central obesity and increased visceral fat, the latter being associated with neck adiposity, increased upper airway fat and metabolic abnormalities, even in normal weight subjects. Sex-related differences in the amount of visceral fat could contribute to the higher prevalence of OSA in males. It is conceivable that OSA and obesity may interact and potentiate their detrimental consequences. OSA-associated metabolic abnormalities have been reproduced in

animal models exposed to a pattern of intermittent hypoxia similar to that found in humans with sleep disordered breathing [50]. However, hypoxia of adipocytes could play an important role in the metabolic disturbances associated with obesity. In addition, OSA and obesity share common mechanisms such as inflammatory activation, oxidative stress and increased sympathetic activity. [51]

The concept that OSA potentially impairs insulin sensitivity (i.e., causes insulin resistance), is a much more recent development. Earliest reports that OSA may impair glucose homeostasis, independent of obesity, began to surface in the early 1990s. [1] However, the lack of preclinical data to guide and support the clinical studies, in addition to the technical difficulties associated with assessing metabolic end points, has hampered progress in the field of OSA and insulin resistance. The measurement of insulin sensitivity, or surrogates of insulin sensitivity, require invasive measurements that are often difficult and technically challenging.

Even the simplest marker of insulin sensitivity, the homeostasis model assessment (HOMA) index, requires measurement of blood glucose and plasma insulin. Other metabolic assessments utilized in OSA patients include the standard clinical assessment of oral glucose tolerance test (OGTT) and the predominantly research-focused, frequently sampled intravenous glucose tolerance test (IVGTT).

The latter test provides several parameters of insulin and glucose homeostasis, including a modeled estimate of insulin sensitivity.

Thus the challenges of measuring insulin sensitivity and other metabolic parameters involved in glucose homeostasis have acted to impede research in this relatively new field. [52]

Prevalence and Incidence of Insulin Resistance - Type 2 Diabetes in OSA

OSA is associated with an increased risk of type 2 diabetes. Whether OSA causes type 2 diabetes or whether it is associated with insulin resistance and diabetes is unclear. Use of CPAP can reverse insulin resistance. Sleep fragmentation, sleep deprivation, and hypoxemia (which all occur in OSA) are thought to play independent roles in glucose intolerance.

Conflicting results show that reversal of glucose intolerance may occur when OSA is treated. The first studies examining the prevalence of glucose dysregulation and OSA appeared in 1993. Since this time, a group of studies, generally involving large epidemiological cohorts, have used questionnaire-based surrogates of OSA, such as snoring or witnessed apnea, and assessed the prevalence or incidence of diabetes based on elevated glucose levels, medication use, or self-reported diabetes. The largest of these studies was a prospective cohort from the Nurses' Health Study (4) that followed 69,852 women without diagnosed diabetes over a 10-yr period. During the course of the 10-yr follow-up period, 1,957 women were diagnosed with the development of type 2 diabetes. The presence of snoring was associated with a 2.25 increase in relative risk of developing diabetes compared with nonsnorers, and the association remained significant after adjustment for covariates including BMI,

activity, smoking, and family history of diabetes. These results indicated that in a large population-based study snoring is independently associated with an elevated risk of developing type 2 diabetes (4). Since snoring is only a surrogate marker of OSA, other epidemiological studies have used polysomnography to objectively classify the presence and severity of OSA. In general, these studies have involved smaller cohorts recruited from clinic populations. Two of the larger studies with clinic-based sample sizes of 250–300 subjects both demonstrated a positive association, independent of obesity, between the severity of OSA and indexes of insulin resistance determined by fasting insulin and glucose. [53] Similar findings were reported by Punjabi et al. from a community-based sample of overweight or obese, but otherwise asymptomatic, males. In this study by Punjabi et al. [54], subjects with mild or moderate to severe OSA had significantly increased odds ratios for elevated fasting and 2-h glucose levels from the OGTT, after adjustment for both BMI and percent body fat. A large community-based pediatric study of 907 children also found a significant association between an AHI of >5 and elevated circulating insulin and HOMA index of insulin resistance. [55] By far the largest epidemiological study to date that directly assessed OSA by polysomnography and measured glucose and insulin levels under fasting conditions and after an OGTT was

based on a subset of 2,656 subjects from the ongoing Sleep-Heart-Health study. In subjects with an AHI of 15 events/h or greater, there were small, but statistically significant, elevated odds ratios of 1.46 for fasting glucose and 1.44 for 2-h glucose levels in the OGTT, after adjustment for age, BMI, waist girth, race, sex, and smoking. In addition, the HOMA index of insulin sensitivity was also significantly elevated in subjects exhibiting an AHI of 15 events/h or greater. In combination, the prevalence data from multiple epidemiological studies support an independent association between OSA and impaired glucose homeostasis. Despite several positive prevalence studies of OSA and indexes of insulin resistance, there is so far only one prospective study examining the association between OSA, determined by polysomnography, and the development of type 2 diabetes. [56] Comparable to previous cross-sectional studies, they showed a positive association between clinically significant OSA and a diagnosis of type 2 diabetes in 1,387 participants in the Wisconsin Sleep Cohort after adjustment for age, sex, and waist girth. However, in a follow-up study of 978 subjects, the odds ratio for developing type 2 diabetes within a 4-yr period for those with an AHI of >15 events/h did not reach statistical significance after adjustment for waist girth. Although many factors may account for the potential disparity between the cross-sectional and longitudinal findings of this

study, the results suggest that epidemiologically there is a lack of strong support for a causal relationship between OSA and the development of insulin resistance and type 2 diabetes. [1]

Effect of Treatment of OSA on Insulin Sensitivity

Nasal continuous positive airway pressure (CPAP) is the predominant therapeutic treatment for OSA and is highly effective at eliminating apneas occurring during sleep. The relationship between the use of CPAP and indices of insulin resistance has been evaluated in several recent studies in OSA patients. The studies have been predominantly of small sample size with subjects recruited from sleep or diabetes clinics; the length of treatment as variable as 1 day to 6 mo; the CPAP intervention uncontrolled with limited adherence data; and few studies utilized the hyperinsulinemic euglycemic clamp as the major outcome variable. In general, the studies were largely negative with variable lengths of CPAP treatment having no effect on fasting insulin levels [57], glucose tolerance [58], or insulin sensitivity. [59] One exception was the 4-mo CPAP trial by Brooks et al. [60], which did show a 32% increase in insulin sensitivity using the hyperinsulinemic euglycemic clamp in subjects with effective CPAP treatment. Thus this initial small and disparate group of

treatment studies did not appear to support the relatively larger body of prevalence studies, suggesting an independent effect of OSA on disrupting glucose homeostasis. However, a more recent and larger study by Harsch et al. in 2004 [61] demonstrated a positive effect of CPAP on insulin sensitivity. In an uncontrolled longitudinal study in 40 OSA patients, insulin sensitivity improved 18% after just 2 days of treatment and by 31% after 3 mo of treatment. Interestingly, a post hoc analysis showed that subjects with a BMI of under 30 kg/m² showed much greater improvements in insulin sensitivity within 2 days of treatment compared with subjects with a BMI at or above 30 kg/m². In a follow-up study in nine of the subjects who were adherent to nCPAP, the improvement in insulin sensitivity was still evident on average 2.9 yr later. [62] Thus the concept has emerged that the detrimental effects of OSA on insulin sensitivity are potentially more apparent in the absence of comorbidities associated with obesity. Interestingly, in a prepubertal pediatric population, the reverse scenario was recently reported in response to a therapeutic intervention. Circulating insulin and the insulin-glucose ratio were significantly decreased 6–12 mo following adenotonsillectomy in obese subjects, but not nonobese subjects. [63] The interaction between the effects of therapy and comorbidities on insulin resistance in OSA will require careful consideration in future studies. A randomized, placebo-

controlled CPAP study by West et al. [64] has recently challenged the positive findings of Harsch et al. Three months of CPAP therapy in patients with known type 2 diabetes and newly diagnosed OSA showed an improvement in measures of sleepiness, but there was no change in HbA1c, HOMA index, or insulin sensitivity as measured by the clamp procedure in either the therapeutic or placebo CPAP groups. A difference between these two conflicting studies is that West et al.[64] used more obese subjects with preexisting type 2 diabetes. However, a similar 6-wk randomized, placebo-controlled CPAP study in non-diabetic patients reported no improvements in metabolic outcomes with therapy, although there was a trend ($P=0.08$) for HOMA to improve by about 15% [65]. Both CPAP studies reported average compliance rates between 3–4 h per night, which may be critical given the report by Dorkova et al. [66] demonstrating significant improvements in HOMA-assessed insulin resistance in CPAP compliant (average 5.07 h/night) but not noncompliant (average 3.49 h/night) subjects after 8 wk. It remains to be seen whether an appropriately powered, placebo-controlled, CPAP study in OSA patients without overt diabetes and long term follow-up can show significant benefits of therapy on insulin resistance. In summary, the clinical evidence for a causal pathway between OSA and insulin resistance remains equivocal. Although prevalence data for an association between OSA and

insulin resistance exists, incidence studies and interventional therapeutic studies have not consistently supported a role for OSA inducing insulin resistance.

Scientific evidence that OSA can lead to insulin resistance

The two pathophysiological characteristics of OSA, intermittent hypoxia and disruption of sleep, can potentially lead to a worsening of glucose homeostasis.

Several epidemiological studies including the Sleep-Heart- Health Study have reported that fasting basal glucose levels, the HOMA index, or blood glucose levels during the OGTT are elevated as a function of the degree of nighttime hypoxemia in OSA. Exposure to chronic hypoxia, as occurs with ascent to altitude, can, at least initially over the first 48 h, lead to insulin resistance. [1] However, by 7 days of exposure to 4.559 m above sea level, insulin sensitivity is correcting back to sea level values. Thus short-term exposure to sustained hypoxia produces insulin resistance in humans, but the acute and IH stress that occurs in OSA may have different metabolic consequences. The potential specificity of the paradigm of hypoxic stress associated with OSA has prompted studies of glucose homeostasis and insulin resistance in rodent models of IH. Interestingly, it appears that glucose homeostasis in mice is a time-dependent phenomena affected by the presence or absence of the IH stimulus.

[67] Since OSA and obesity frequently coexist, the disruptive effects of IH stress on glucose homeostasis may be potentially exacerbated by adiposity. The comorbid impact of obesity was examined in a rodent model of IH. Genetically obese *ob/ob* mice exhibited increasing basal insulin levels associated with impaired glucose tolerance over a 3-mo period of exposure to IH compared with weight-matched control *ob/ob* mice. The confounding or interacting effects of obesity have likely contributed to much of the inconsistency in the clinical literature where comorbidity associated with obesity is often present. Recently, techniques have been developed to assess the impact of experimental IH on glucose homeostasis in healthy humans free of OSA and metabolic dysfunction. The study by Louis et al. [68] showed that a 5-h period of experimental IH in normal sleeping humans (20–30 hypoxic events/h) decreased insulin sensitivity, as assessed by the IVGTT. These data on humans, in combination with studies on mice, suggest that acute exposure to IH can cause insulin resistance in both humans and animals even in the absence of comorbid conditions. In addition to hypoxic stress, impaired sleep is also a potential candidate for metabolic dysfunction. [1] There are also several prospective epidemiological studies, including the large Nurses Health Study mentioned above, demonstrating that short sleep duration increases the risk of developing diabetes. Furthermore, sleep

deprivation can reduce leptin levels and increase ghrelin levels, potentially acting to stimulate appetite. [1] Thus the impact of sleep deprivation on compromising metabolic function may be exacerbated by a secondary effect to increase appetite, which itself may lead to weight gain and further metabolic dysfunction. Sleep disturbances, such as deprivation or restriction, may not reflect the disturbances in sleep that occur in OSA. Typically, total sleep time is not significantly restricted in OSA, but rather sleep is fragmented by frequent microarousals. The study by Stamatakis et al. [69] attempted to model the sleep fragmentation of OSA by arousing normal healthy humans from sleep over two nights (30–40 times/h) using auditory and mechanical stimuli. This form of experimentally induced sleep fragmentation caused a 20.4% decrease in the insulin sensitivity index as assessed by the IVGTT. There does not appear to be any comparable animal models of sleep fragmentation that have demonstrated metabolic abnormalities. Clearly there is a need for more clinical and translational research to determine whether sleep fragmentation can contribute to the development of insulin resistance. [1]

Prospects for future

Evaluated the social and health impact of obesity, with all the metabolic consequences resulting from it, and the fact frequently coexists with sleep disturbances, we need more studies of the incidence of insulin resistance and type 2 diabetes in well characterized patients with polysomnographic determination of OSA. Similarly, long-term studies are needed on the use of CPAP and to evaluate the therapeutic efficacy. In particular, there is need for studies that can investigate how the use of CPAP, which eliminates and improve breathing disorders during sleep, can make reversible insulin resistance and type 2 diabetes.

The effectiveness of CPAP for improving insulin sensitivity should be compared quantitatively with the insulin- sensitizing effects of pharmacological therapies and behavioral therapies of weight loss and physical activity. Study designs need to become more comprehensive with respect to multiple sampling across the day and night, as well as controlling potentially confounding factors such as food intake and physical activity.

However, despite all these challenges, the issue that restricts progress the most is the overriding and pervasive influence of obesity in both metabolic disorders and OSA.

Solving the algebraic equation “ Z_X ” and extracting the Z component from

Syndrome X is proving extremely difficult. Whereas animal models can provide unique insights and control for the effects of obesity, ultimately discoveries need to be translated back into the clinical arena.

All data in the literature suggest that respiratory disorders that occur in OSA can have an independent action, but each action represents the tip of the iceberg supported by insulin resistance and obesity

QUICKI and HOMA Index

Patients with type 2 diabetes are frequently obese, and often have OSA. It is therefore not surprising that a significant number of patients suffer from both conditions [70, 71, 72]. A common feature of both diseases is insulin resistance. It is well known that in diabetic patients insulin resistance have a great impact on metabolism, together with other factors that are partly genetically determined. Insulin resistance is able to disturb the glycaemic balance and cause hyperglycaemia. As already mentioned, there is a growing body of data suggesting that the insulin sensitivity in non-diabetic patients with OSAS can be improved by nasal CPAP therapy. Given this fact, it seems possible that the glycaemic control in patients with diabetes and OSAS could also be improved. [73]

Insulin resistance contributes significantly to the pathophysiology of type 2 diabetes and is a hallmark of obesity, dyslipidemia, and other components of the metabolic syndrome . Therefore, it is necessary a simple method for assessing insulin sensitivity and changes made after any therapeutic interventions for epidemiological studies, clinical investigations and clinical practice.

The hyperinsulinemic - euglycemic glucose clamp is the primary reference method for assessing insulin sensitivity in humans because it directly measures the effects of

insulin in promoting glucose utilization . The glucose clamp is a complicated technique and overly invasive procedure that can still be suitable for small research so that they now rarely used for large-scale assessments in clinical practice. Therefore we consider a group of indexes in place to assess insulin sensitivity or insulin resistance . The indices are derived from the simpler levels of fasting glucose and / or insulin and include the values of fasting insulin and HOMA (homeostasis model assessment) .

There are also several other indices for the assessment of insulin sensitivity based on the oral glucose tolerance test . Other indices are based on protocols that provide the infusion of glucose and insulin of varying complexity. Among these, the much used is the "frequently sampled intravenous glucose tolerance test " (FSIVGTT) . It has recently come into use the "*quantitative insulin - sensitivity check index index*" (QUICKI), which is determined by a mathematical formula which considers the levels of fasting glucose and fasting insulin. This index used in non-obese patients, obese, diabetic or hypertensive gave results comparable to the glucose clamp method better than all the other indices such as HOMA. In a large number of clinical conditions that include type 2 diabetes, gestational diabetes , hypertension, polycystic ovary syndrome, and liver diseases, the QUICKI index can roughly assess any

changes in insulin sensitivity after various therapeutic interventions. In an analysis of subjects with insulin resistance QUICKI index is the best method to replace the glucose clamp in terms of predictive power for the onset of diabetes. [74]

QUICKI index is calculated , as mentioned above, from the levels of fasting glucose and insulin. QUICKI : $1 / [\log ([I.sub.0]) + \log ([G.sub.0])]$ where $[I.sub.0]$ is fasting insulin (μ/ml) and $[G.sub.0]$ fasting glucose mg / dL.

The HOMA index is calculated as: $[G.sub.0] (mmol / l) \times [I.sub.0] ([\text{micro}] U/ml) / 22.5$.

Intermittent hypoxia in OSA and diabetes

The desaturation–reoxygenation sequence is a typical pattern coupled with the majority of respiratory events. This sequence, defining intermittent hypoxia, leads to oxidative stress, with production of reactive oxygen species (ROS) [75]. Numerous studies have shown increased oxidative stress using various biological markers, although comorbid conditions such as diabetes, hypertension and obesity may account for some of these results [76]. The increased levels of ROS contribute to the generation of adhesion molecules, activation of leukocytes and production of systemic inflammation. Together, these mechanisms generate vascular endothelial damage and dysfunction. [77] Moreover, high sympathetic output, as consistently found in OSA, may lead to insulin resistance, even in nonobese OSA patients [78], representing an additional source of oxidative stress. [4] Oxidative stress is characterised by an imbalance between the production and degradation of ROS. Although numerous studies have addressed the issue of increased ROS production, there are only a limited number of studies addressing the role of antioxidant capacities in OSA patients. Barcelo et al. reported an alteration in antioxidant capacities, with a reduction in total antioxidant status, and a decrease in both vitamin A and E levels. In the same study, continuous positive airway pressure (CPAP) treatment normalized

total antioxidant status [79]. In 2008, impairment of albumin antioxidant properties independent of body mass index (BMI) and related only to OSA severity has been demonstrated [4, 80].

OSAS , a syndrome that leads to repeated intermittent hypoxia phenomena , is frequently associated with insulin resistance and diabetes often in obese subjects generally, although the underlying mechanisms of this association are still largely unknown . In a study of obese rats were used to examine the effects of intermittent hypoxia on insulin resistance . From the results obtained it was initially highlighted a decrease of glucose levels, but an increase in insulin levels in the blood. In obese mice also exposure to intermittent hypoxia for a longer period (12 weeks) , has led to increased levels of fasting insulin in a time dependent or with insulin levels rise according to the weeks of exposure hypoxia. [81] Recent studies also show that OSA is independently associated with insulin resistance and fatty liver (fatty liver) . This suggests that OSA may also alter hepatic metabolism of lipids. In fact, some studies conducted in rats have shown that obese OSA and intermittent hypoxia -induced determine an up - regulation of several genes that control the synthesis of cholesterol and fatty acids , the synthesis of phospholipids and triglycerides . In conclusion intermittent hypoxia may exacerbate liver alterations (fatty liver), already typical of

obesity, through the activation of genes that increase the biosynthesis of sterols [82] .

The assessment of the high risk of metabolic syndrome associated with intermittent hypoxia is further confirmed by further studies that correlate the obstructive sleep apnea , characterized by their intermittent hypoxia with an increased risk of high cholesterol, with an increase in the biosynthesis of triglycerides and phospholipids and a reduction in the hepatic uptake of cholesterol, hypertension, obesity and insulin resistance. [4]

Chronic intermittent hypoxia , typical of obstructive sleep apnea is associated with a substantial damage cortico-hypothalamic which leads to a deterioration of neurocognitive functions , respiratory and cardiovascular system. Previous studies in animal models (rats) have shown that chronic intermittent hypoxia leads to apoptosis in cortical neuronal cells, although the exact sequence of the mechanisms underlying these events remains unknown . The oscillation of the values of O₂ concentration during intermittent hypoxia appears to be similar to the phenomenon of ischemia/re-oxygenation and could further increase the cellular production of reactive oxygen species . The increase of oxygen radicals in mice was further confirmed by an expression of typical markers of oxidative stress or c Fos , c Jun, NF KB in cortical cells of guinea pigs . The long-term exposure to intermittent hypoxia in mice leads to

an increase of oxidative phenomena interesting proteins, nucleic acids , lipid peroxidation of the membrane and to increased expression of caspase- 3 which have a pro-apoptotic activity . Moreover, transgenic mice exposed to chronic intermittent hypoxia, with increased expression of superoxide dismutase , have a reduction of neuronal death just for reduced oxidative activity. In conclusion these results suggest that the increase of reactive oxygen species, mediated by intermittent hypoxia contribute, at least partially, to apoptosis of neuronal cell and neurocognitive dysfunction. [83]

From this, OSAS may also contribute to neuronal damage at central level.

Furthermore recent studies have shown that sympathetic nerve activity and blood pressure are generally elevated in patients with sleep-disordered breathing . As we have seen above the increase of sympathetic activity is closely correlated with an increased risk not only of hypertension but also of insulin resistance . In fact, sympathetic activity increase, due to typical microarousal of patients with OSAS, may be the main cause of insulin resistance that is as a prelude to type 2 diabetes

Evaluating , therefore, several epidemiological studies , and considering that one of the main risk factors for insulin resistance and diabetes is obesity, as well as it is for OSA, it is evident that the majority of patients who have frequent phenomena of

intermittent hypoxia , and then obstructive sleep apnea often being obese, they run a higher risk of developing a real metabolic syndrome in which insulin resistance and diabetes are the most important events.

Today, there is another important emerging interpretation of intermittent hypoxia typical of SDB. In this study, it has been inferred that intermittent hypoxia stimulates the development of adaptive responses, called preconditioning. This process is mediated at least partially by a genetic reorganization, through a hypoxia inducible factor, which leads to a process of long-term adaptation and is responsible for the increase of the levels of endothelial growth factors, erythropoietin, atrial natriuretic peptide , and nitric oxide. The synthesis of a neurotrophic factor participates in the control of neuronal plasticity after hypoxia. So the mechanisms of neuroprotection against intermittent hypoxia may be the result of an action in vascular and neurological level . The majority of the considered factors involved in the development of the mechanisms of neuroprotection are also present during sleep in patients with obstructive apnea , which are frequently exposed to severe degrees of hypoxia . It seems that the OSAS represents a clinical example of preconditioning and the development of adaptive responses to intermittent hypoxia. [84]

Materials and Methods

Polysomnography

In the study were examined 174 consecutive patients with snoring evaluated in our sleep laboratory .

All patients underwent standard overnight polysomnography , performed using a computerized laboratory system (Compumedic S-Series Sleep System , Abbotsford , Australia) , according to the criteria suggested by the American Thoracic Society [85]. During recording , the following parameters were measured : 4 -lead electroencephalographic (EEG), airflow (nose - mouth), the movements of the rib cage and abdomen and O₂ saturation .

Apneas were defined as complete cessation of airflow for at least 10 seconds associated with oxygen desaturation of 4% or greater, and divided into obstructive or central in the presence or absence of respiratory movement, respectively. Similarly the hypopnea was defined as the reduction in airflow of at least 50% associated with desaturation equal to or greater than 4% .

The diagnosis of OSAS was placed when apnea/hypopnea index (AHI) was equal to or greater than 10.

Metabolism of glucose

In patients we measured the levels of glucose (g / L) and insulin (μ U / ml) in the blood. The blood sample for the measurement of these parameters was carried out only once.

Insulin resistance

In patients with insulin resistance values were obtained by the homeostasis model assessment (HOMA), calculated using the following formula:
$$\frac{\text{insulin (mU / ml)} \times \text{glucose (mmol / l)}}{22.5}$$

Insulin sensitivity

The values of insulin sensitivity in our patients were obtained using the "quantitative insulin sensitivity check index" (QUICKI), calculated using the following formula:

$$1 / (\log (\text{fasting insulin}) + \log (\text{fasting glucose}))$$

Other metabolic parameters

In patients were also measured the levels of total cholesterol (mg / dl) , the levels of HDL cholesterol (mg / dl) , the LDL cholesterol levels (mg / dl) and trigliceridi (mg / ml) .

Statistical Analysis

Data are presented as \pm standard error of the mean (SEM).

Comparisons between groups were performed by a Student's t test for unpaired data

Results

Of the 174 patients (122 males and 52 females) , 115 (72 % male) had an AHI greater than or equal to 10 (range 10-106) . The remaining 59 (65 % male) had an AHI of less than 10 were used as controls . The OSAS patients (age 54.1 ± 1.48) had an average value of AHI of 45.5 ± 2.4 (SEM) and controls (age 51.1 ± 2.4) had an AHI of 5.7 ± 0.8 . Patients with OSAS had a BMI of 31.6 ± 1.8 and 29.7 ± 1.8 controls . The average nocturnal oxygen saturation among patients with OSAS was 92.2 ± 0.4 and 95.2 ± 0.3 in controls .

The values of glucose in the blood were higher in OSAS patients than in controls (1.08 ± 0.04 g / L vs 0.88 ± 0.04 g / L), insulin levels (18.1 ± 2.6 μ U / ml vs. 8.5 ± 1.4 μ U / ml), and the HOMA index (4.78 ± 0.8 vs 1.99 ± 0.7). Instead there were substantial differences in the values of total cholesterol (187 ± 3.8 vs 190 ± 11.3) and in the HDL fractions (41.2 ± 1.0 vs 43.0 ± 4.7) in both LDL (120 ± 3.4 vs 127 ± 9.0). The results are different for triglycerides (137 ± 2.8 vs. 95 ± 1.1).

In total, the proportion of patients with hypercholesterolemia was higher in OSAS patients than in controls ($P < 0.05$).

The percentage of patients with hypertriglyceridemia was significantly higher in patients with OSAS than in controls ($P < 0.05$). Insulin resistance ($\text{HOMA} > 2.4$) was higher in OSAS patients than in controls ($P < 0.05$), as well as BMI values were higher in patients with OSAS than in controls ($P < 0.05$).

The results showed that the risk factors for insulin resistance ($\text{HOMA} > 2.45$) were predominantly the BMI (OR 2.4, 95 % CI 1.3-4.6, $P < 0.001$), OSA (OR 4.0, 95 % CI 1.6-9.7, $P < 0.001$) and hypertension (OR 2.3, 95% CI 1.2-4.3, $P < 0.001$).

Revealed no correlation with sex, age, hypercholesterolemia and hypertriglyceridemia.

We did a multiple regression in which the OSAS (OR 2.7, 95 % CI 1.2-3.70, $P < 0.05$) and BMI (OR 2.3, 95% CI 0.29-2.70, $P < 0.05$), but not hypertension (OR 1.8, 95% CI 0.8-6.0, $P > 0.8$) were independent risk factors for insulin resistance. From the correlation between insulin levels and OSAS we got a positive relationship between insulin and AHI ($r = 0.32$, $P < 0.001$) and insulin levels and BMI ($r = 0.43$, $P < 0.001$).

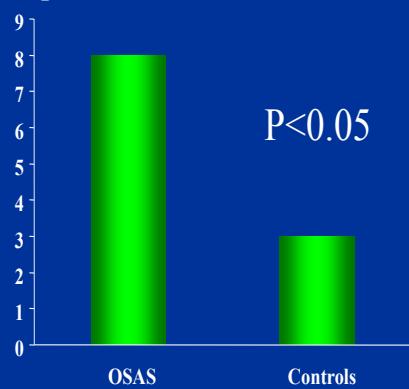
Tab. 1 Characteristics of the patients

	OSAS	Controls	P
	N=115	N=59	
ETA'	54.1±1.48	51.1±1.4	NS
Sesso (m)	72%	65%	NS
AHI	45.5±2.4	5.7±0.8	<0.001
BMI	31.6±1.8	29.7±1.8	NS
nSaO2(media%)	92.2±0.4	95.2±0.3	<0.05

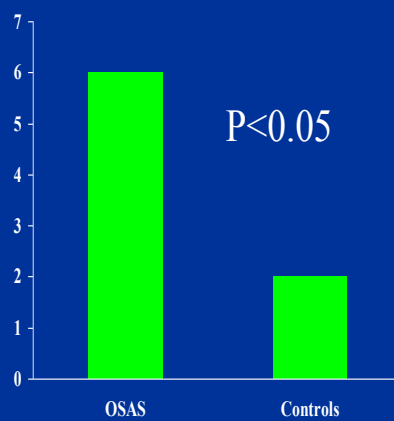
Tab.2 Metabolic Data

	OSAS	Controls	P
F-Glucose	1.08±0.4	0.88±0.4	<0.05
F-Insuline	18.1±2.6	8.5±1.4	<0.001
HOMA	4.78±0.8	1.99±0.7	<0.05
QUICKI	0.325±0.08	0.368±0.01	<0.05
Cholesterol(mg/dl)	187±3.8	190±11.3	NS
HDL (mg/dl)	41.2±1.0	43.0±4.7	NS
LDL (mg/dl)	120±3.4	127±9.0	NS
Triglycer. (mg/dl)	137±2.8	95±1.1	<0.05

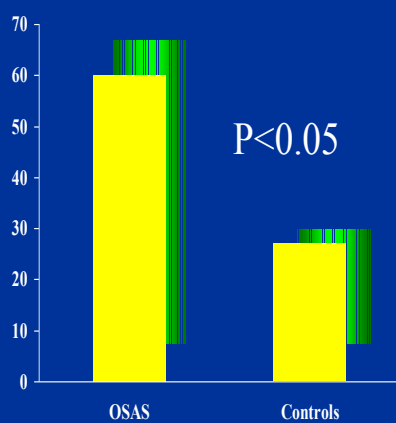
% Ipercolesterolemia



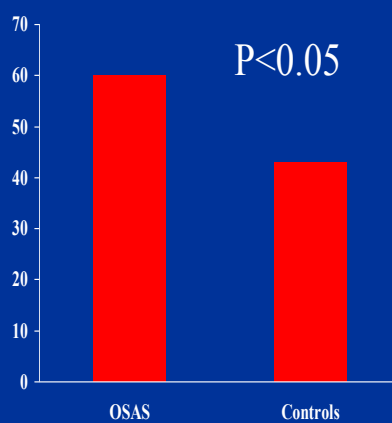
% Ipertrigliceridemia



% Insulino resistenza (HOMA>2.4)



% BMI>30



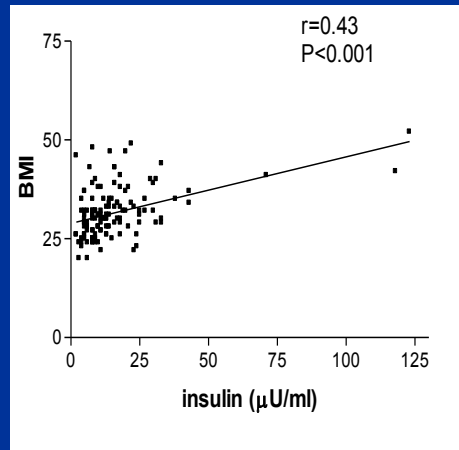
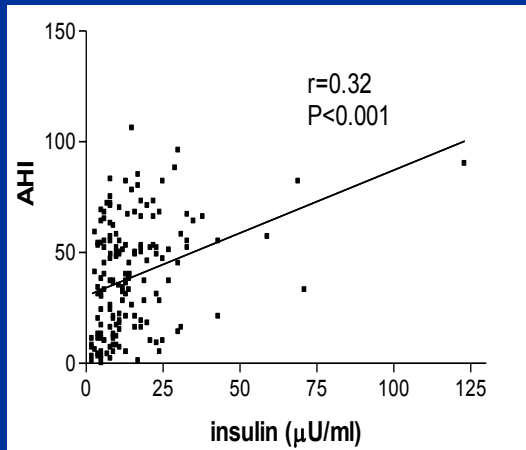
Tab.3 Risk factors for insulin resistance

	Odds Ratio	95% CI	P values
Sex	0.7	0.3±1.4	0.3
BMI	2.4	1.3±4.6	<0.001
OSAS	4.0	1.6±9.7	<0.001
Age (>50)	1.5	0.8±2.8	0.1
Hypertension	2.3	1.2±4.3	<0.001
Hypercholesterolemia	0.81	0.2±2.6	0.9
Hypertriglyceridemia	1.2	0.3±4.6	0.7

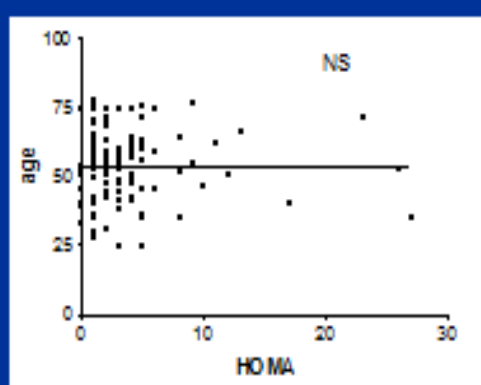
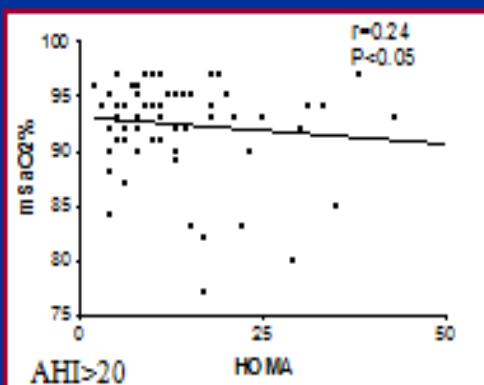
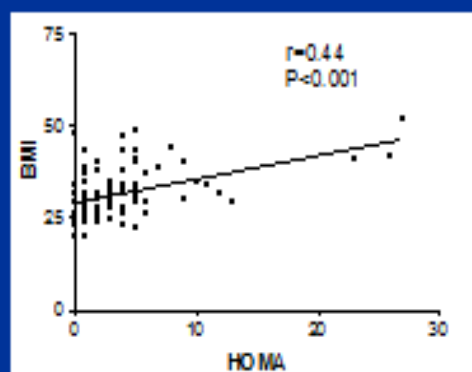
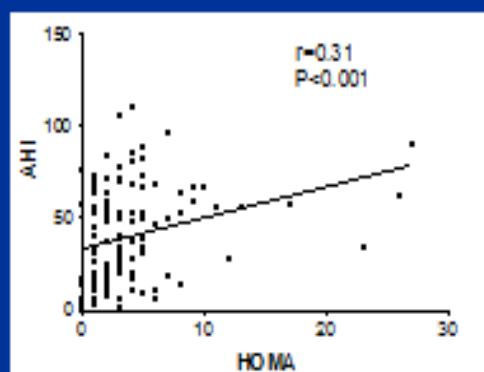
Tab.4 Risk factors for insulin resistance – Multiple logistic regression

	Odds Ratio	95% CI	P values
OSAS	2.7	1.2±3.70	<0.05
BMI	2.3	0.29±2.70	<0.05
Age	1.0	0.96±5.0	0.8
Hypertension	1.8	0.8±6.0	0.8

Correlation between insuline and OSAS



Correlation between insulin resistance and OSAS



Discussion

From the results obtained from our study we can conclude that the severity of insulin resistance correlates with the severity of obstructive sleep apnea . Obesity may be a risk factor, add up or act synergistically in causing insulin resistance .

So it seems likely that both obstructive apnea and obesity can be considered as risk factors for insulin resistance .

Considering that the severity of insulin resistance correlates with an increased risk for type 2 diabetes, there is a predisposition to the establishment of this metabolic disease.

We have also seen how even obesity correlates with an increased risk for obstructive sleep apnea and also for insulin resistance. In fact, obesity favors the onset of metabolic alterations and variations anthropometric parameters which are risk factors for OSA.

From our work results that the major part of the patients examined have at the same time obesity, insulin resistance and OSAS , and then the main risk factors for metabolic syndrome.

The observation of our patients also shows the importance that plays hypertension as a risk factor for insulin resistance. In the multiple regression analysis between the major risk factors, however, hypertension seems to correlate short, at least compared

to OSAS and BMI , in the determinism of insulin resistance.

Therefore OSAS and BMI are the main risk factors for insulin resistance and possible metabolic changes: mainly glucose intolerance and subsequently type 2 diabetes.

In addition, the number of cases reported in the literature shows that the typical nocturnal micro-arousals in patients with OSAS can cause a temporary but repeated adrenergic activation that can interfere with insulin secretion during sleep.

Sympathetic activation due to micro-arousals correlates to an increase of the average values of blood pressure, with the possibility of developing hypertension, in patients with OSAS and SDB.

In conclusion, therefore, the results obtained in our study shows the importance of considering that patient with metabolic syndrome are often obese and with SDB and in particular with OSA. Therefore, these patients are always characterized by insulin resistance with the possibility of type 2 diabetes, hypertension and dyslipidemia (linked to obesity, but also to insulin resistance).

Considering all the studies in the literature, the links between obesity, SDB and insulin resistance are not fully clear yet, even if it appears now clear a close bond between them as essential components of the metabolic syndrome.

Our study demonstrate that sleep apnea is an independent risk factor for insulin resistance and, the severity of insulin resistance correlates with the severity of sleep apnea and obesity.

It is likely that both sleep apnea and obesity may concur to the altered glucose metabolism.

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