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Obstructive Sleep Apnea (OSA), an emerging health problem

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Abstract

Obstructive Sleep Apnea (OSA) is the most common respiratory disorder in Western societies: according to a first recent worldwide epidemiological study, it was estimated that 936 million patients aged 30-69 years with mild to moderate OSA and 425 million patients aged 30-69 years with severe OSA requiring CPAP treatment.
Recently, the Centre for Research on Health and Social Care Management (CERGAS) at the Bocconi University of Milan has estimated that in Italy, the prevalence of moderate to severe OSA occurs in the 27% of the general population, with an overall prevalence of mild to medium-severe OSA of more than 24 million people aged between 15 and 74 years (54% of the adult population), while from a practical point of view, Italian doctors diagnosed only 460.000 moderate-severe patients (4 per cent of the estimated prevalence) and 230,000 patients were treated (2 per cent of the estimated prevalence), highlighting a substantial gap between diagnosis and treatment.
In addition, OSA patients are often obese and the close correlation between the two conditions suggests that the prevalence of OSA will increase in the short term as obesity increases. At the individual level, OSA leads to a significant decrease in quality of life (HRQoL) and intellectual and mechanical/functional capacities with reduced physical activity, as well as a marked increase in sudden death and risk of cardiovascular and metabolic diseases.
Emerging epidemiological data also suggest that the severity of OSA associated with the severity of chronic nocturnal hypoxemia (CIH) correlates with an increased risk of diabetes mellitus, metabolic syndrome (MS) and cancer. OSA is also an important risk factor for high blood pressure, acute and chronic atrial fibrillation (FAC), chronic coronary artery disease (CAD) and stroke.
It is therefore intuitive that at the social level, OSA also leads to a decline in economic productivity.
This article addresses OSA from a new epidemiological perspective, according to the latest prevalence studies, and addresses emerging problems related to the diagnosis.

Keywords: obstructive sleep apnea, OSA

1. Introduction

Obstructive Sleep Apnea (OSA) is defined as a very common disorder in the general population characterized by loud and habitual nocturnal snoring with repetitive upper airway obstruction (apnea) (Paul E Peppard et al. 2013; Heinzer et al. 2015) sometimes accompanied by daytime sleepiness. The severity of OSA is generally measured by the Apnea-Hypopnea Index (AHI) which defines the number of nocturnal respiratory pauses (apnea) or partial and/or incomplete pauses (hypopnea) and/or obstructive events measured per hour of sleep.
The diagnostic definition of OSA is obtained from both polysomnography recording (PSG) from which the AHI index, which must be ≥5 events/hour of sleep, and from the night-time

cardio-respiratory monitoring (MCRN). In the best-known American epidemiological study, called the Wisconsin Sleep Cohort Study, the prevalence of OSA in the general American population was estimated to be around 24 percent in men and 9 percent in women between 30 and 60 years of age (Punjabi 2008)
Current prevalence predictions indicate a worldwide increment and suggest that OSA is present in both developing countries and Western societies (Kapur 2010)
New data from a first worldwide epidemiological study published in August 2019 on Lancet carried out in 16 countries, and from the analysis of the results of 17 new epidemiological prevalence studies, all carried out with the new instrumental diagnostic criteria of the American Academy Sleep Medicine (AASM) of 2012 (new diagnostic definition of hypopnea and arousal) suggest that the prevalence of the disease worldwide can be estimated at around 936 million patients with mild to moderate OSA, (almost one billion!) aged 30-69 years and 425 million patients with severe OSA aged 30-69 years who need night-time CPAP treatment (Benjafield et al. 2019)

2. OSA and obesity: a close relationship

Obesity is an epidemic disease with a rapid progression in Western society (Armeni et al. 2019). Obesity, defined as body mass index (BMI) >30, is the most important risk factor for the onset of OSA, in particular when the fat distribution is prevalent in the thoracic-abdominal area. In the multi-center Wisconsin Sleep Study, it is reported that in OSA patients body weight gain over a 4-year period is an important predictor of OSA progression; the study showed that in OSA patients, a 10 percent increase in body weight resulted in a 32 percent increase in the AHI metric index, with a relative 6-fold increase in the risk of developing an even more severe form of OSA (Paul E. Peppard et al. 2000) Another multicentre epidemiological study, Sleep Heart Health Study, conducted on native Americans over 65 years of age, also showed that a 10 kg weight gain over a 5-year observation period resulted in a 2.5-fold increase in AHI with a 5.2 percent increase in the risk of developing OSA-related cardiovascular disease (Newman et al. 2005)
In addition, according to another epidemiological study carried out in bariatric surgery, OSA is present in 41 percent of patients with BMI >28 and 78 percent of severe obese patients with BMI >35 who have to undergo bariatric surgery (Domenico Maurizio Toraldo et al. 2013; Lopez et al. 2008). In obese patients with severe OSA, obesity is considered responsible for sleep deprivation and changes in sleep architecture, which leads to comorbid insomnia, which worsens the quality of sleep and life of obese OSA patients (Spiegel et al. 2005). The alterations of the diet and of the alimentary style in paediatric age, can determine alterations of the neuro-hormonal regulation of leptin and greline that can favour, with the years, the development of OSA. A series of clinical studies have demonstrated in the obese OSA patient the presence of elevated serum levels of functionally altered neuro-hormonal leptin; leptin is a hunger inhibitor and intervenes in the regulation of body weight together with greline and affects the neurological centers of breathing during sleep; treatment with continuous positive airway pressure (CPAP) determines an improvement in serum leptin levels with an improvement in obesity and respiratory activity during sleep (Chen et al. 2015; Phillips et al. 2000; Ong et al. 2013).
Recently, a longitudinal controlled clinical study was conducted in Sweden on more than 3,400 severely obese patients with OSA, using laparoscopically adjustable gastric banding to reduce body weight in severe OSA. In this study, the decrease in BMI resulted in a marked improvement in OSA symptoms (quality of life and daytime sleepiness) and in a decrease in the use of drugs for the treatment of diabetes mellitus 2 (DM) and metabolic syndrome (MS). In another clinical study of severe obese patients (BMI >35) with severe OSA (AHI >30/hs), bariatric surgery resulted in significant weight loss and a decrease in OSA severity evidenced by a reduction in AHI from 80 to 17.7 ±10.0 obtained after about 5 months of surgery (Dixon, Schachter, and O'Brien 2005) However, the majority of OSA patients who underwent bariatric surgery, after surgery, after about 6 months demonstrated a significant residual OSA (AHI >15) at a control PSG, and special attention should be paid in the protocol for the repetition of PSG in the follow-up of operated

patients and for CPAP treatment if the AHI index should be >10 (Greenburg, Lettieri, and Eliasson 2009; Lettieri, Eliasson, and Greenburg 2008). Leptin is therefore a hormone involved in appetite suppression, it is released from adipocytes located in abdominal fat and is produced in proportion to the abdominal fat content (Münzberg and Morrison 2015); it acts on respiratory centers to stimulate ventilation in response to peripheral hypercapnia in OSA with the aim of reducing the increased PaCO2 and normalizing PaO2. Physiologically ineffective leptin increase has been associated with worsening of OSA and metabolic syndrome (D M Toraldo et al. 2015; Kalra 2008).

3. Genetic factors

The OSA recognizes multiple predisposing factors of a genetic family type. Given the complexity of the syndrome, it is not possible to recognize a single genetic factor that can determine its manifestation, but a set of genetic-biological factors. The risk of OSA is genetically predisposed in 40% of cases (Kent, Ryan, and McNicholas 2010; Redline and Tishler 2000).
The prevalence of OSA in first-degree relatives of OSA patients ranges from 22 to 84 percent (Mathur and Douglas 1995). Anatomical risk factors for OSA, such as obesity and structural changes in the soft tissues of the upper first airway such as macroglossia and mandibular hypoplasia, show familiarity. Obesity and upper airway alterations often occur from early childhood and studies of monovular twins have shown 57-86 percent heritability from early youth (Silventoinen and Kaprio 2009)
Another study in a Scottish population identified a strong family genetic component for OSA and suggested that hereditary craniofacial malformations were more important than obesity itself (Mathur and Douglas 1995). Indeed, the morphology of the pharyngeal lateral wall, the properties of the craniofacial mucosa and neck fat have a significant level of heritability and therefore susceptibility for OSA.

4. Economic aspects and quality of life

OSA has a significant economic impact on Western public health systems and must be considered and managed as a chronic condition and not, as is the case in Italy, as an acute pathology (the recognition of chronic pathology implies the adoption of an ad hoc government law). OSA is burdened by direct costs, which are the healthcare costs necessary for the diagnosis and treatment of the disease and the associated comorbidities as well as for the use of hospital admissions, and by indirect or social costs, very high, due to a reduction in work productivity, permanent disability due to road or work accidents. This is compounded by the overall economic impact of the OAS, which is very high.
In the United States, according to an article by the American Academy Sleep Medicine (AASM) of 2016 (Nieto et al. 2012) the annual cost for an undiagnosed OSA patient is estimated to be around $5,500 (considering direct and indirect health care costs), while in diagnosed OSA patients it drops to $2,100 per year (Campos-Rodriguez et al. 2013b) Patients with sleep disorders are less productive than those without such disorders and have a higher level of absenteeism and decreased productivity at work due to fatigue, chronic fatigue and excessive daytime sleepiness (Sherman 2013) Occupational accidents are also more common in patients with OSA (Alghanim et al. 2008) Several studies have shown that the quality of life measured with QOLi questionnaires is unfavourable in OSA patients compared to non-OSA patients and improves after various medical, ventilatory, dental and surgical therapies (Alghanim et al. 2008; Smith and Shneerson 1995; Jenkinson, Stradling, and Petersen 1997). The bedfellow of an untreated OSA patient may also suffer from insomnia due to loud snoring at night. The QOLi of the untreated snoring OSA patient's bed partner significantly improves when the OSA is successfully treated (Gall, Isaac, and Kryger 1993; Parish and Lyng 2003).

5. OSA and cardiovascular disease

The strongest scientific evidence supporting an independent role for OSA in the promotion of early atherosclerosis and the development of adverse cardiovascular outcomes (cerebral strokes, myocardial infarction and complicated vascular aneurysm) can be found in clinical

studies addressing the relationship between OSA and arterial hypertension (Paul E. Peppard et al. 2013) . There are controlled clinical trials that have shown a correlation between OSA severity and the likelihood of developing hypertension with its complications (Hedner et al. 2006; Javier Nieto et al. 2000)
Recent European data show that out of 11,900 patients participating in the European study called Cohort Apnea Study (ESADA), chronic intermittent nocturnal hypoxemia with deep desaturations is a predictive factor for early vascular atherosclerosis and that it can be a key factor for the development of arterial hypertension and early vascular endothelial damage (vascular aneurysm) (Tkacova et al. 2014). The results of another clinical study have shown an increased propensity in OSA patients for the development of hypertension and cardiovascular complications (P E Peppard et al. 2000). In another epidemiological study, carried out on 709 subjects, the presence of severe OSA conferred a very high risk to diagnose hypertension, regardless of other factors such as diet, obesity and smoking history. Other recent clinical data from a Spanish study also confirmed this same relationship (José M. Marin et al. 2012; Kent et al. 2013)
With regard to chronic ischemic heart disease with CAD, recent data suggest that CAD is very widespread in patients with OSA and constitutes about 30 percent of patients with CAD, and vice versa that patients with CAD are more likely to develop an obstructive pathology during sleep type OSA (Mooe et al. 1996). In another epidemiological study called Health Study carried out on more than 6,000 patients, the severity of CAD (measured as atherosclerotic plaque diameter) was correlated to the severity of the AHI metric index (SHAHAR et al. 2001)
In addition, patients with OSA are at high risk of developing paroxysmal atrial fibrillation (FAP); in another study involving 566 patients with chronic ischemic heart disease, severe OSA was found and this was associated with a fourfold probability of developing FAP (Mehra et al. 2006).
In OSA patients, the increased diameter and size of the left cardiac atrial chamber determines an increased presence of risk factors for the appearance of FAP and subsequent failure of the subsequent pharmacological cardioversion (Drager et al. 2010). In addition, recurrence of FAP becomes less likely if it is significantly reduced with the initiation of CPAP treatment (Kanagala et al. 2003). Obstructive sleep pathology is also an independent predictor of ventricular arrhythmia, particularly in subjects with chronic heart failure (Monahan et al. 2012).
OSA is much more common in patients who have had a recent stroke or transient ischemic attack such as TIA, in 32-63 percent of patients compared to the general population, and is associated with increased mortality and worse functional outcomes over time (Bassetti and Aldrich 1999; Good et al. 1996). In addition, the prevalence of cerebrovascular disease seems to increase with increasing severity of OSA. Some prospective studies suggest that the presence and severity of OSA is a predictive factor for stroke (Arzt et al. 2005; Yaggi et al. 2005; Redline et al. 2010).

6. OSA and cancer

The fundamental pathophysiological mechanism that characterizes OSA is represented by chronic nocturnal intermittent hypoxia (CHI) that generates a chronic inflammatory cascade that causes a diffuse vascular epithelial damage of pro-atherogenic type (Garvey, Taylor, and McNicholas 2009) the same chronic inflammatory mechanism could promote the development of cancer through the release of angiogenic factors.
In a murine model of OSA, the possibility of developing malignant tumors towards blood or skin cells (malignant melanoma) by triggering mechanisms of systemic inflammation, oxidative stress and immune dysregulation has been demonstrated (Isaac Almendros et al. 2013). Data from these animal models suggest that exposure to CIH in humans may determine the origin of malignant cellular neoformation and increase distant metastatic progression and spread (I Almendros et al. 2012; Nieto et al. 2012)
Therefore, several longitudinal clinical studies in humans have been proposed that have assessed the association between OSA and cancer. In an analysis of 1,522 patients participating in the Wisconsin Sleep Cohort Study, subjects with severe OSA were at almost five times the

risk of developing cancer (Campos-Rodriguez et al. 2013a). Similarly, in another Spanish clinical study of nearly 5,000 OSA patients, the severity of the disease expressed by the intensity of nocturnal hypoxemia predicted the development of malignant neoplasms in different body districts (Kendzerska et al. 2014). A Canadian retrospective cohort study has shown that there is a close relationship between OSA and cancer, and among other things within this population an independent association between smoking-related cancer and severity of chronic nocturnal hypoxemia has been demonstrated (Young et al. 1993). To date, no data have been published about the effect of CPAP therapy on cancer, and potentially innovative clinical trials are being conducted in this area.

7. Diagnosis Considerations

Clinically defined OSA syndrome in combination with excessive daytime sleepiness (ESD) and obesity is estimated to increase in the coming years in both women and men due to increased obesity (Al Lawati, Patel, and Ayas, n.d.) OSA, a chronic disease, if left untreated is associated with an increase in overall mortality and a number of serious social and health consequences such as reduced quality of life, reduced productivity in the workplace and increased road and work accidents (De Benedetto, Garbarino, and Sanna 2017; Jose M. Marin et al. 2005)

The gold standard diagnostic investigation is complete, stationary polysomnography (PSG) with neurological and video-surveillance electrodes that is performed in a sleep laboratory (LS) and is the preferred method to diagnose OSA correctly and completely (D M Toraldo et al. 2017). The treatment, not pharmacological, is the application of CPAP device (continuous positive pressure in the upper airway) which is performed in LS with high health care costs (manual night titration supported by a neurophysiology technician). Due to the high costs and long waiting times to perform the examination, new simplified but equally suitable and important methods for home sleep testing (HST) have been developed. These are low-cost, portable and non-permanent instruments, defined as polygraphs (night cardiorespiratory monitoring, MCRN) which, in addition to making the diagnosis, also offer the possibility of home treatment by self-titling positive airway pressure (APAP). A number of studies compared the complete polysomnography performed in LS with HST, confirming the diagnostic non-inferiority of the latter, and also validated home treatment with CPAP device. The diagnostic and therapeutic non-inferiority of HST vs LS has also been confirmed by other studies (D M Toraldo et al. 2017)

The metric index expressed as AHI/hs is used to diagnose the degree of OSA severity by polygraph/polysomnography recording. A distinction is made between mild (5-15 events/hour), moderate (15-30 events/hour), severe (>30 events/hour) and very severe (>60 events/hour). A threshold value of 5 is considered a sign of normalcy in adult patients.

In the case of AHI <5 the patient can be considered negative for the diagnosis of OSA, unless the daytime sleepiness symptom is present, in which case the patient should undergo LS night polysomnography (doubtful cases). The test is considered positive for the diagnosis of OSA if AHI ≥5 (2,16,17).

In conclusion, OSA (Passàli et al. 2014; Costa and De Benedetto 2017) leads to impairment of quality of life, increased risk of cardiovascular and metabolic complications and poor work performance as well as the possibility of causing road and work accidents.

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