12

Chronic Obstructive Pulmonary Disease and Diabetes *Mellitus*

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1. Introduction

The progressive increase in the average age of the population leads to chronic diseases that are increasingly important. Chronic conditions are large in number, the prevalence of each one is high and so does the annual cost of their care. Moreover, clinicians alert about the impact of one disease on the development and severity of others. Among chronic morbidities the most prevalent are cardiovascular disease (CV), cancer, diabetes *mellitus* (DM) and chronic obstructive pulmonary disease (COPD) (Chillón et al., 2009). Noticeably, a 25% of patients older than 65 years have two chronic conditions and this figure rises to 40% in population over 75 years old (Chatila et al., 2008).

The following text focuses on two of these pathologies: COPD and DM. Our group provided data on COPD pathophysiology, particularly about hypoxia and related oxidative stress, the effect of nutritional status, physical exercise and sleep disorders (Álvarez-Sala R, 2010; García-Río et al., 2009, 2011; Braghiroli & Álvarez-Sala, 2010; Alcolea et al., 2007). In addition, the sleep apnea hypopnea syndrome (SAHS), its association with metabolic syndrome (MS) constituents and the sum of SAHS plus COPD in the so called "overlap syndrome" were studied (Santiago-Recuerda et al., 2007; De Miguel et al., 2002). We made a search in PubMed including articles published during the last ten years about COPD and DM, in order to review how one disease influences the onset, evolution, treatment and prognosis of the other one.

2. Chronic obstructive pulmonar disease and diabetes *mellitus* definitions, epidemiology and comorbidities

COPD is defined as a preventable and treatable entity caused by toxic gases, mainly tobacco. Its main feature is poorly reversible obstruction of airflow that is progressive and is associated with a systemic inflammatory response (Álvarez-Sala, 2010). This proinflammatory state may lead to extrapulmonary manifestations (Global initiative for obstructive lung disease [GOLD], 2008) in the majority of patients have a negative effect on the overall prognosis of the disease (Peces Barba et al., 2008). Its prevalence sharply

increases with age and tobacco consumption, and is estimated at around 4-10% globally (Mathers, 2008). Nowadays this disease is considered the fourth leading cause of death and the WHO assessed that in 2020 ranked third in terms of mortality and the fourth in prevalence. In Spain there have been two major studies on the prevalence of COPD. On the one hand we have the IBERPOC study that estimated a 9.1% in patients aged between 40 and 70 years. Most recently EPI-SCAN obtained a 10.2% in subjects between 40 and 80 years (Álvarez-Sala, 2010). In recent years, COPD is considered a disease that goes beyond the lungs involvement. The high morbidity associated with this condition makes some authors (Álvarez- Sala,2010; Sevenoaks et al., 2006; Oudijk et al., 2003) think that pulmonary disease is just an expression of a multisystemic inflamatory disease. The main comorbidities associated with COPD are diabetes, hypertension, ischemic heart disease and heart failure. In addition, other illnesses converge such as malnutrition, osteoporosis, anemia, endocrine disorders, depression or anxiety (Moussas et al., 2008). Most of the comorbidities influence prognosis and length of hospital stay for these patients. One example is low weight, defined as a body mass index (BMI) below 18.5 kg/m^2, and considered a predictor of poor prognosis in patients with COPD. In particular, loss of muscle compartment is the most affected in the body and its measurement is a better predictor of mortality than total body weight. Another important aspect is osteoporosis, which is present in up to 68% of patients with severe COPD, with a consequent increase in fracture risk. There are several risk factors that may influence the development of osteoporosis in these patients: age, malnutrition, weight loss, smoking, hypogonadism, sedentary lifestyle or the use of glucocorticoids.

In addition, patients with more severe lung disease, have endocrine alterations, the most frequent is exogenous hypercorticism that associated with hyperglycemia, infections and cardiovascular complications (Chillón et al., 2009).

With reference to DM, it is a frequent consequence of corticosteroid therapy in individuals with advanced COPD and those receiving high and continued doses. However, coincidence with primary diabetes predominates in COPD patients, even if we assume there is no linkage between both diseases. There are two types of primary diabetes, type 1 is characterized by absolute insulin deficiency secondary to an autoimmune cause in 90% of cases or idiopathic destruction of pancreatic beta cells. These patients require insulin to survive. Type 2 DM is far more frequent in COPD. The natural history of type 2 begins with insulin resistance with a compensatory hyperinsulinemia that maintains normal glucose tolerance at the outset. Persistent insulin resistance facilitates the final expression of a latent β cell dysfunction thus resulting in hyperglycemia and frank diabetes. Diabetes has become one of the most prevalent health problems in recent years, according to some authors, affect over 366 million people worldwide in 2030 (Wild et al., 2004).

3. Links between chronic obstructive pulmonary disease and diabetes *mellitus*

At this point, the question arises about the relationship between both disorders. To answer this question, we will refer to the so called cardiovascular risk of COPD. COPD and DM are associated with an enhanced cardiovascular risk profile. COPD patients have a two to three-fold cardiovascular related mortality when compared to the general population rates. Cardiovascular disease is the second cause of death among COPD patients and the first one

among patients with DM. COPD predisposes to pulmonary hypertension, right ventricular dysfunction and arrhythmias. DM is often accompanied by systemic hypertension, left ventricular dysfunction and congestive heart failure. Carotid and peripheral atherosclerosis are also macrovascular complications of DM. Finally, both COPD and DM converge in a higher occurrence of coronary events and sudden death (Falk et al., 2008).

Probably all these comorbidities are influenced by the inflammatory and oxidative stress in these patients after exposure to tobacco (Lavi S et al., 2007). One hundred million people will be affected by tobacco during the XXI century. The tobacco is currently responsible for five million and six hundred thousand deaths each year worldwide. It acts synergistically with other risk factors and may increase cardiovascular mortality by 20, but after leaving tobacco for two or three years, the risk is superimposed to non-smokers.

The prognostic significance of hyperglycemia in these patients has been evaluated in several studies, especially during exacerbations. It seems that the poor glycemic control increases hospital stay, the isolation of gram-negative bacteria in sputum, increased pulmonary artery pressure and the risk of death (Archer & Baker, 2009; Gudmundsson et al., 2006; Makarevich et al., 2007; Sicras et al., 2007; Parappil et al., 2010). Moreover, it seems that sustained hyperglycemia may have other effects that worsen the prognosis. The vascular damage should be highlighted in the first place. Microvascular diabetic disease may affect the alveolus-capillary barrier. Pulmonary microvascular involvement may worsen respiratory function in patients with COPD and DM. Pulmonary diffusing capacity in patients with type 1 or type 2 DM is decreased and this decrease may be more pronounced in those with other microvascular complications.

It is known that early diagnosis and treatment of COPD and its comorbidities, including DM, have prognostic implications. However, the association and interactions between COPD and DM are not completely understood. Under the current evidence, coincidence is more plausible than a causative connection. Whether causality exists or not, the high rate of simultaneity in general population will give ground for concern. We consider that DM affects 1.6 to 16% among subjects with COPD. DM prevalence increases in relation with pulmonary impairment, older age and BMI of 30 kg/m2 (Lavi et al, 2007).

Pathogenic links between COPD and DM have been hypothesized in the setting of population-based and clinical observational studies. The Atherosclerosis Risk Assessment in Communities (ARIC) and the Fremantle Diabetes Study (FDS) found a lung vital capacity declining in persons with type 2 diabetes (Yeh et al., 2008; Davis et al., 2004). Lung dysfunction was predominantly restrictive, while COPD is an obstructive disorder. Excessive weight could be an explanation as mean BMI of diabetic patients (30.9 ± 5.7 kg/m^2) significantly exceeded BMI of the non diabetic group (27.2 ± 4.8 kg/m^2) in the ARIC study. DM patients who subsequently developed COPD also had a higher BMI in data by Ehrlich et al. (Ehrlich et al., 2010). A theoretical risk for COPD in a diabetic environment is based on several mechanisms: glycation of proteins of lung parenchyma and bronchial tree, thickening of basal lamina, increased susceptibility to infections and a modified sarcolema with subsequent skeletal muscle weakness (Weynand et al., 1999; Dalquen, 1999). Nevertheless, hyperglycemia has mostly been associated with a modest restrictive defect due to diabetic microangiopathy that thickens the epithelial and capillary basement membrane. The result is an increased extracellular matrix and connective tissue and an altered alveolar diffusion capacity of the lungs (Popov & Simioescu, 1997).

Conversely, development of DM once COPD has been diagnosed was also shown by Mannino et al. (Ford & Mannino, 2004; Mannino et al., 2008). Again, more than 60% of patients with COPD and DM were overweight or obese. Stronger evidence of the COPD-DM association comes from the Nurses Health Study (NHS) that involved 97,245 30-55 year old female nurses, 1,342 of whom reported COPD (Rana et al., 2004). The risk of DM among COPD patients was statistically significant (RR 1.8, 95%CI 1.1-2.8) despite the scarce number of incident diabetes cases (n = 19) and after exhaustive adjustment for covariates. It has to be said that a detection bias can not be ruled out in NHS and other cited studies. Besides, among other limitations, data from NHS could only be generalized to median-age Caucasian women. Nevertheless, this study provides the best evidence available due to the homogeneous anthropometry and lifestyle habits of the nurses enrolled including smoking, dietary and exercise, and because of the long-term prospective follow-up.

Beyond diabetes itself, glycemic exposure seems to be relevant. Severity of hyperglycemia was a negative predictor of a reduced lung volume in the FDS. With reference to COPD, a complementary analyses by Ehrlich et al. (Ehrlich et al., 2010) showed the disease was more prevalent among poorly controlled diabetic patients, with an hazard ratio of 1.03 (95%CI 1.01-1.04) per each unit increase in baseline glycated hemoglobin (A1C). To the date, diabetes has not been proven to be a determinant factor for COPD exacerbations, but poor glycemic control is a risk factor of pneumonia related hospitalization in type 1 and type 2 diabetes *mellitus* (Kornum., 2008). Consistent with this findings, in vitro studies under hyperglycemic conditions have shown an abnormal neutrophil function such impaired chemotaxis, phagocytes and bacterial killing (Pozzilli, 1994, as cited in Ehrlich et al., 2010).

We can assume there is a high proportion of undiagnosed glucose intolerance, obstructive and restrictive lung disorders. Thus, one possibility is that untreated diabetes contributes to pulmonary dysfunction and that non diagnosed decreased lung function favors diabetes development in predisposed patients (Davis et al., 2004). Once diabetes is evident, a vital capacity loss was found in the ARIC study. An 8% different FVC in diabetic compared to nondiabetic subjects was found in the Copenhagen City Heart Study (Heindl et al., 2001). The baseline difference was similar in ARIC, but further declining linked to diabetes was not found after 15 years of follow-up. In contrast, more rapid declines of FVC and FEV1 were observed in patients with higher baseline A1C in FDS. Tobacco may contribute to explain these differences. A secondary analysis of diabetic individuals in the Framingham Cohort Study found that the decrease in pulmonary function, with a restrictive pattern, was greater in smokers than in never smokers, inferring that diabetes may increase susceptibility to the adverse pulmonary effects of smoking. A similar interaction was proposed in the NHS (Rana et al., 2004; Walter et al., 2003).

To add complexity, sleep apnea hypopnea syndrome is often added in many of diabetic patients. SAHS is mainly secondary to obesity and is also associated with an increased insulin resistance. There have been several studies linking SAHS and DM. This relationship could be based on a common point such as obesity. In this sense, members of the Wisconsin Sleep Cohort were followed for four years. It was demonstrated that patients with an AHI ≥ 15 had an increased risk of developing diabetes type 2 (odds ratio 2.3 [1.28 to 4 11], adjusted for age, gender and body habitus) (Watz et al., 2009). In the same line, longitudinal follow-up of the cohort of Affairs Connecticut Healthcare System Veteran concluded an independent association between SAHS and incidence of new cases of diabetes type 2

(hazard ratio: 1.43 [1.10 to 1.86], adjusted for age, gender, race, fasting glucose, BMI and weight change) (Reichmuth et al., 2005).

A further step would be the association of COPD and SAHS in the same individual or "overlap syndrome". The prevalence of overlap varies depending on SAHS clinical or subclinical definition. The latter identifies individuals with at least 5 hypopneas or apneas per hour during a polysomnography or polygraphy whom diurnal sleepiness does not necessarily occur. The prevalence of SAHS is estimated to be 1-4% in general population. The percentage of overlap is 3-11% among subjects with SAHS and 16-20% among COPD patients (Owens & Malhotra, 2010; Zamarrón et al., 2008). COPD clinics is characterized by cough, sputum production and dyspnea. Most common symptoms of SAHS include loud snoring, excessive daytime sleepiness, personality changes and deterioration of quality of life. Overlap syndrome is characterized by older, more hypoxemic and hypercapnic patients with higher mean pulmonary pressure and similar or less BMI as compared with single SAHS. Thus, the overlap syndrome is a singular entity that may allow a deeper knowledge of the interactions between COPD, SAHS and glycemic-metabolic related disruptions.

4. Chronic obstructive pulmonary disease and diabetes *mellitus* related pathogenesis

COPD and DM share relevant features in their genesis and course. Hypoxia, insulin resistance, oxidative stress and inflammation are the basis of a common pathogenesis. Concomitant factors such as tobacco, obesity and sleep disorders merge in endothelial dysfunction and atherosclerosis leading to a high cardiovascular risk of both conditions (Figure 1).

Inflammation is a well recognized phenomenon in COPD and DM pathogenesis. In COPD, inflammation and oxidative stress require an energy expenditure that exacerbate the pre-existing hypoxia. In a parallel way, inflammatory cytokines exacerbate insulin resistance through diverse mechanisms. Impaired function of the type 1 insulin receptor substrate (IRS-1) is a key, direct mechanism. Thus, there is a chronic, subclinical inflammation at the background of COPD and DM. The question about its significance in patients with simultaneous COPD and DM is then arised. Being not fully clarified, we propose the following sequence of events: common COPD and DM related pathogenesis would start by hypoxia and insulin resistance followed by systemic inflammation, oxidative stress and a final coexistence of endothelial dysfunction and subsequent cardiovascular events.

4.1 Hypoxia

Hypoxemia and also hypercapnia, though in a less extent, are a stimulus for the hyperactivation of the sympathetic nervous system. In this setting, the activity of the sympathetic system is sustained in a non-resting anomalous way (Ashley et al., 2010; Heindl et al., 2001; Raupauch et al., 2008). Sustained hypoxia in COPD is an important central sympathetic system drive. A higher and long-lasting muscle sympathetic nerve activity (MSNA) is seen in COPD patients. Its direct consequence is a permanent vasoconstriction of the muscle vessels. Ashley et al. did not only show a sympathetic burst of multiple neurones, but they also graded the intensity of the response. The method used was the measurement of the firing probability and mean firing rates of single muscle vasoconstrictor

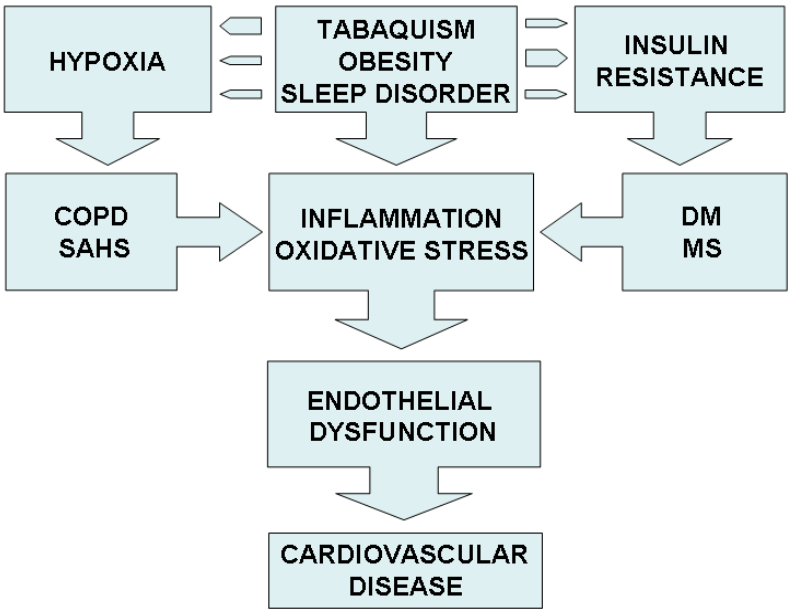

Fig. 1. Convergent pahogenesis of chronic obstructive pulmonary disorders, diabetes *mellitus* and metabolic syndrome. COPD: Chronic obstructive pulmonary disease; SAHS: Sleep apnea-hypopnea syndrome; DM: Diabetes *mellitus*; MS: Metabolic syndrome.

neurons. These authors observed a general and markedly higher sympathoexcitation in COPD patients when compared to SAHS, bronchiectasis or healthy subjects. The individual neurone firing probability and mean firing rate were comparable to those recorded in SAHS, but higher than those observed in the healthy group. This finding suggests that muscle vasoconstrictor response is sustained long-after intermittent hypoxia, as it would occur in SAHS patients. Permanent vasoconstriction causes further resistance to the airway flow in any chronic obstructive disorder that is not completely reversed by normoxia. With respect to DM, the noradrenalin liberation of spontaneously active neurons has also been observed in the isolated disease.

Obesity also increases the MSNA burst incidence, but at lower levels than those seen in COPD or SAHS. Multiple firing of single-unit neurones has not been shown in obese subjects. Advanced age neither seems to be an explanation for the MSNA hyperactivity linked to COPD.

4.2 Inflammation

Systemic inflammation is a common bound between COPD and DM. Both conditions are a proinflammatory state characterized by transcription and expression of hypoxia-induced factor 1 (HIF-1) and increased levels of serum inflammatory cytokines such as C-reactive protein (CRP), interleukin (IL) 1, IL-6 and tumor necrosis factor α (TNF-α) (Archer & Baker 2009). C-reactive protein (CRP) and the nuclear factor NF-κβ pathway are important mediators of the inflammatory response in this context (McNicholas, 2009).

CRP is a type I phase protein with the ability to bind the bacteria surface facilitating the fixation of complement that mediates bacterial killing and/or phagocytosis. CRP stimulates further cytokine production mainly through macrophages activation. TNF-α, IL-1 and IL-6 stimulate CRP synthesis by inducing its hepatic gene expression. NF-κβ is the master regulator of TNF-α, IL-8 and other cytokines transcription and synthesis. TNF-α and other cytokines are produced by monocytes and leukocytes and are enhanced by hypoxia in vitro studies (Takabatake et al., 2000 in Sevenoaks & Stockley, 2006).

TNF-α pathway is related with the deterioration of accessory muscles involved in ventilation. TNF-α induces loss of fat-free mass in COPD patients with subsequent loss of skeletal muscle function. Muscle wasting is also directly mediated by nuclear factor-κβ (NF-κβ) that inhibits the MyoD gene expression. MyoD regulates myofibril synthesis and repairs. Secondly, TNF-α interaction with its receptor can activate muscle and other cellular apoptosis. Reduced IGF-1 and testosterone levels are also adjuvant factors leading to muscle wasting (Sevenoaks & Stockley, 2006).

CRP is a marker of COPD exacerbations and elevated pulmonary pressure in the stable disease (Zamarrón et al., 2008). If we look at the intermittent side of the obstructive disease, CRP is not identified as a prognostic marker of SAHS after adjustment for BMI. TNF-α pathway is related with muscle wasting and pulmonary hypertension commonly developed in COPD disease. NF-κβ and HIF-1 pathways are closely related and may have a differential role in chronic and intermittent hypoxia. Indeed, HIF-1 seems to have a predominant role in COPD, while NF-κβ pathways may predominate in the intermittent hypoxia of SAHS. TNF-α levels can be predicted by the oxygen desaturation index in SAHS. Its levels are increased with independence of obesity (McNicholas, 2009). The prognostic value of these markers in overlap syndrome is unknown.

4.3 Oxidative stress

Now considering the cellular immune response, the leucocitary drive in COPD is a fountain of reactive oxygen species (ROS). The oxidative response advocates a protein, lipid and DNA damage within the cell. Oxidative stress influences NF-κβ cascade through mitogenesis activating protein kinases (MAP-k) perpetuating inflammation this way.

On the inverse loop, TNF-α stimulates ROS production. Indeed, an additional ROS-related mechanism seems to exacerbate TNF-α and NF- κβ effects on muscle wasting (Oudijk, 2003). TNF-α and ROS act in multiple ways. They have a common source in circulating leukocytes. Activation and dysfunction of leukocytes is shared by COPD, SAHS and DM. The activated leukocyte enhances the expression of adhesion molecules such as CD11b and CD18. This effect predominates in lung tissue if we look at COPD, while systemic endothelium is the main target in SAHS. In addition, exacerbations of COPD may deteriorate the antioxidant response, while ROS are particularly enhanced in SAHS when hypoxia is intermittent in a similar way to injury reperfusion syndrome (McNicholas, 2009). Because ROS production is also a direct effect of hyperglycemia, oxidative stress can be posed as a link between SAHS, DM, overlap syndrome and metabolic syndrome. MS is not so clearly identified in the particular case of COPD. A specific oxidative response in SAHS/ overlap may well account for this difference.

Another effect of neutrophil dysfunction is the inactivation of antiproteases leading to airspace ephitelial damage and mucus hypersecretion. As we see, TNF-α / neutrophil axis is

a key in maintenance of the lung COPD phenotype. Finally, advanced COPD stages are characterized by cachectic patients who have an impaired metabolism of proteins, lipids and carbohydrates that is thought to be the maximum expression of systemic inflammation and oxidative stress.

The different pathways involved are complex and the available knowledge on their confluence is still limited. We need to clarify if the mentioned markers of hypoxia, inflammation and oxidative stress have a predictive value of the highest morbidity and mortality in patients with COPD and DM. Moreover, COPD and DM cannot be fully understood if we do not consider classical risk factors, mainly tabaquism in COPD genesis, and obesity in DM. The influence of sleep architecture is an emerging aspect related to DM and hardly studied in COPD with the exception of the overlap syndrome (Zizi et al., 2010). The effect of age and physical activity should also be considered in the COPD and DM interaction. Among these factors, lately research has focused on obesity, sleep disorders and their consequences on respiratory and metabolic environments.

4.4 Insulin resistance and obesity

The inflamed adipose tissue is a well recognized trigger of insulin resistance. A theoretical link between COPD related inflammation and DM could be the switch to a protein depleted and more adipose skeletal muscle. This change of composition inside the sarcolema induces peripheral insulin resistance in the human organism. Such impairment is not necessarily reflected in a visceral fat excess or in obesity (Festa et al., 2002). If present, both conditions aggravate the risk for diabetes.

Then, obesity could be the cause of insulin resistance in patients with lung obstructive disorders. However, obesity does not seem to be the only mediator of insulin resistance. We need to consider a reduction of glucose uptake mediated by hypoxia. Under hypoxemic conditions, insulin resistance has been proved in both obese and lean mice (Polotsky et al., 2007). An explanation could be the hypoxia mediated sympathetic hyperactivity. But sympathetic hyperactivity does not seem to be the unique source of insulin resistance either. Indeed, pharmacologic blockage of autonomic nervous activity did not reverse the insulin resistance under intermittent hypoxia in animal models (Tasali et al., 2008). As we previously mentioned, oxidative stress is a plausible link between the cyclic hypoxia-reoxygenation phenomenon in SAHS and insulin resistance. A first argument is that oxidative stress entails glucose and lipid peroxidation. Secondly, it enhances the inflammatory status through activation of NF-κβ and reduction of nitric oxide bioavailability. Oxidative stress helps to understand why a link between hypoxia and DM seems to be stronger in SAHS than in COPD despite a more sustained and profound hypoxia in the latter. Nevertheless, experimental data about hypoxia and glucose metabolism under mimic SAHS and COPD conditions are still very limited.

The role of obesity in COPD is not established. However, and despite not being the only pathway, obesity is a clear line of causality between SAHS and type 2 DM. Indeed, obesity is the main risk factor for SAHS and type 2 DM. In data from the American National Sleep Foundation, high risk for SAHS is present in one out of four adults and in 57% of obese individuals. The proportion of mild or mild to moderate SAHS attributable to excess weight is 58% (Tasali et al., 2008). Some controversial results have been obtained regarding obesity.

Two epidemiological studies have suggested that obesity is the unique or main cause of insulin resistance in SAHS patients (Reichmuth et al, 2005; Stoohs et al., 1996). However, there is growing evidence about alternative links between SAHS and type 2 DM (Tasali et al., 2008). In terms of SAHS severity, only one study had a prospective design and assessed SAHS by polysomnography. An independent relationship between SAHS severity and glucose intolerance was not found after adjustment for body habitus, although the duration of follow up was only four years (Reichmuth et al., 2005).

SAHS itself aggravates obesity through several mechanisms that also enhances insulin resistance: neuroendocrine dysregulation and physical inactivity. Neuroendocrine dysregulation includes an enhanced ghrelin and leptin secretion. Hyperleptinemia has been proposed as a previous step to insulin resistance even in the absence of weight gain. Indeed, leptin was the only upregulated gene affecting glucose uptake in both obese and lean mice exposed to intermittent hypoxia (Polotsky et al., 2007). Hyperleptinemia may also be a marker of SAHS severity (Pillar & Shehadeh, 2008). Physical exercise increases after CPAP treatment of SAHS. However, the reversal of the insulin resistance by CPAP is controversial (Pillar & Shehadeh, 2008).

Ten out of thirteen clinical based studies suggested a body habitus non-related association between SAHS and insulin resistance or glucose intolerance (Tasali et al., 2008). Three studies considered waist-to-hip ratio because central fat distribution seems to be a more relevant mediator of insulin resistance than BMI (Sharma et al., 2007; McArdle et al., 2007; Tassone et al., 2003). There was a positive association in two out of three. In a similar fashion, three studies found higher HOMA-IR and fasting glucose after adjustment for visceral fat measurements (Kono et al., 2007; Makino S et al., 2006; Vgontzas et al., 2000).

Deposit of neck and abdominal fat alter the regular mechanics of ventilation. The most relevant accumulation of neck fat is located inside upper-airway muscles of the pharynx, this way changing the lumen to an oval shape. Also, abdominal fat exerts a mass effect that reduces the distension of the chest walls resulting in a decreased thoracic and tracheal traction during inspiration (Pillar & Shehadeh, 2008).

To conclude with, the impact of obesity on COPD disease is not as clear as the impact on SAHS. An overall role for obesity in SAHS is a common finding despite the diversity of ethnic and geographical origins of the studied subjects. We also have reasons to think that obesity, with its mechanical and metabolic effects, may impair COPD course, particularly in initial GOLD stages and/or overlap syndrome.

4.5 Sleep disorders

As an additional mechanism, obesity favors insulin resistance and SAHS development through sleep disturbance. Sleep curtailment, sleep fragmentation and a subsequent disrupted signalling lead to unbalanced energy expenditure and far too much appetite. Recent research proposes impaired sleep as a source of metabolic disturbances in SAHS and overlap syndrome patients.

Sleep disturbances are an invariable feature of COPD and SAHS patients. Both chronic and intermittent hypoxemia get worse during sleep. Sleep influences ventilation even in normal subjects due to: a reduced response to the hypoxic drive, a reduced ventilatory efficacy of

hyperrelaxed accesory muscles and upper-airway dilators and, finally, because lung residual capacity is reduced during sleep and so the pharyngeal traction is. Then, normally decreased nocturnal oxygen saturation becomes a challenge in COPD and SAHS patients. A more blunted chemical response to hypoxic drive is seen in both diseases. A diminished ventilation/perfusion quotient results from an hyperinflated lung, less activity of intercostal muscles and a dissociated diaphragmatic and intercostal activity in COPD patients. A collapsible pharynx is the main cause of hypoxia and sleep disturbance in SAHS. Associated symptoms, comorbid diseases, drugs and sedentary lifestyle also reduce sleep efficacy.

Evidence from extent population-based prospective and experimental studies links short and/or poor sleep and type 2 diabetes (Tasali et al., 2008). The sleep-related diabetes is not necessarily explained by apneas (Ayas et al., 2003; Mallon et al., 2005). Two laboratory studies performed in healthy young lean adults obtained an enhanced insulin resistance and a diminished insulin secretion related to sleep deprivation (Knutsonet al., 2007; Spiegel et al., 1999). Measurements of insulin-glucose homeostasis were based on intravenous glucose overload and minimal model technique respectively. Minimal model (Bergman, 2005) resulted in a glucose disposition index (DI) 40% lower than after sleep recovery. A low DI reflects an insulin secretion that is insufficient to compensate for insulin resistance. A low DI indicates a high risk for type 2 DM. Subjects underwent a relative short sleep restriction (4 h for 6 or 2 nights) however inducing a pre-diabetic state similar to the habitual in older adults. Reduction of slow-wave sleep and sleep fragmentation were assessed in another laboratory set-up (Tasali et al., 2008), resulting a similar marked decrease in insulin sensitivity without a balanced insulin secretion. The decrease in insulin sensitivity was correlated with a rise in heart rate variability as a measure of the daily sympathetic activity. In addition, insulin resistance was more related to sleep slow wave suppression than to sleep fragmentation. These experimental procedures have not been reproduced in specific SAHS and COPD settings.

We conclude that, in addition to hypoxia, sleep curtailment enhances sympathetic activation. Noradrenalin is a counter-regulatory hormone that reduces insulin release and function. There is also a decreased glucose uptake by muscle cells favored by high evening cortisol levels and extended duration of elevated growth hormone (GH) levels at night. Another relevant effect of short sleep is upregulation of appetite. A hormonal deregulation of appetite has been observed in the mentioned laboratory studies (Knutson et al., 2007). Ghrelin and leptin are hormones that exert respective hunger and satiety effects. Leptin inhibits appetite, modulates fat distribution and increases energy expenditure. Sleep debt shortens the adequate time that leptin levels require to balance the previous onset of a ghrelin peak. The ghrelin peak occurs during the first half of the night. An attenuated function of leptin due to leptin-CRP boundage has also been hypothesized (Chen et al., 2006). It is plausible in an inflammatory scene such sleep debt.

In diabetic patients, sleep duration and quality was associated with a poorer glycemic control in data from a cross-sectional study on African-American adults with type 2 DM (Knutson et al., 2006). Sleep characteristics were self-reported. Interestingly, sleep quality was associated with poorer glycemic control only in patients with chronic complications of diabetes. A theoretical explanation would be an impaired autonomic response at the background of those diabetic subjects. They would be more susceptible to a less-quality sleep. The cited results were adjusted for age, gender, insulin treatment and BMI. Central

obesity and respiratory conditions were not initially considered. Regarding these items, the authors found an association between A1C levels and sleep duration and quality that remained stable after excluding patients at high SAHS risk. Of note, the highest mean A1C was observed in those with higher versus lower risk for SAHS (9.7% vs. 7.9%, $p < 0.01$).

In an inverse direction, poor glycemic control and obesity are associated with a less quality of sleep. Intervention studies are needed to precise the sense of causality. To take into account, as a final insight sleep dept is a novel habit that could influence the exponential increase of diabetes, obesity and SAHS in our worldwide societies.

5. Metabolic syndrome

We can consider three group of factors in COPD patients: respiratory exacerbations and lung function, nutritional and muscle disorders and finally metabolic syndrome. There are several definitions of MS, but a common element is that all the components are related to the existence of insulin resistance, which will lead to glucose intolerance, abdominal obesity, elevated triglycerides, decreased HDL cholesterol and hypertension. It is estimated that 40-50% of individuals over 60 years have MS in industrialized countries. In Europe there is a prevalence of 15% (Hu et al., 2004; Botros et al., 2009). In a study of 170 patients with COPD and 30 with chronic bronchitis, Sicras et al. (Sicras et al., 2007) observed that the frequency of MS was 53%, 50%, 53% 37% and 44% in patients with chronic bronchitis, COPD I, II, III and IV respectively. They explained the lower incidence in the latter stages of the disease would be related to weight loss.

As previously mentioned, insulin resistance and the development of type 2 diabetes is the key point of MS. In this sense, we have discussed that hypoxia, obesity and sleep disturbances reduce the insulin sensitivity. We could say that the association between SAHS and DM resembles the clustering of metabolic diseases found in MS. The components of MS keep bidirectional links, such insulin resistance and obesity, that are plausible between SAHS and DM. Similarly, the sum of SAHS and DM may result in multiplied cardiovascular effects.

We discussed that the association between COPD and MS is far less clear than the parallel course of SAHS and MS. Due to hypoxia, a change towards multiple firing of vasoconstrictor neurons will increase noradrenalin levels, so we could expect at least arterial hypertension in COPD. Surprisingly, patients were not hypertensive in data by Ashley et al. (Ashley et al., 2010), and the authors posed tempering vascular factors that might balance the hypertensive drive. The links between COPD, metabolic syndrome and cardiovascular disease are largely unknown. Most of the data available deals with the association between SAHS, endothelial dysfunction and subsequent cardiovascular morbidity (Zamarron et al., 2008). There is also recent evidence of an increased mortality in overlap patients without CPAP therapy as compared to COPD (42.2 vs. 24.2%, $p < 0.001$) (Marin et al., 2010). Death was most commonly due to cardiovascular disease. A poorer quality of life was also demonstrated, even in patients without diurnal sleepiness.

The COPD, SAHS and DM shared inflammatory state perpetuates these chronic conditions and have a cardiovascular impact. Hypoxia induced factor (HIF-1) triggers inflammation and angiogenesis inside the atherosclerotic plaque this way facilitating the entry of phagocytes, red blood cells and lipoproteins. CRP is also directly related to atherosclerosis.

CRP interaction with Fcgamma receptor (Fcγ R) possibly increases the monocyte chemokine MCP-1 production, leading to monocyte adherence on to the arterial wall (Sevenoaks & Stockley, 2006). CRP also facilitates the production of foam cells that give shape to the atherosclerotic plaque. The "Third National Health and Nutrition Examination Survey" (NHANES III) denoted an association between CRP and myocardial ischemia. CRP levels higher than 3 mg/dl are significantly related to future cardiovascular events (Pai et al., 2004). This level is commonly surpassed in COPD patients. NF-κβ and TNF-α pathways leading to cardiovascular disease deserve a thorough research in COPD, SAHS and overlap syndrome. TNF- α induces the expression of CRP in the liver, being at the core of the process. TNF- α also has an active effect on macrophages migration, adhesion and differentiation within the atheroma plaque (Sevenoaks & Stockley, 2006). During COPD acute exacerbations, a further rise in CRP levels is also followed by a rise in fibrinogen as the expression of a thrombosis risk. Of note, cardiovascular mortality is particularly enhanced within and following hospital admission for an acute exacerbation (Sevenoaks & Stockley, 2006; Smeeth et al., 2004).

Briefly, the common consequence of COPD, SAHS, MS and DM is an inflammatory status that culminates in endothelial dysfunction leading to cardiovascular events. A novel explanation for the convergent endothelial dysfunction is a depletion or low response of bone marrow stem-cells. This phenomenon determines a reduction of circulating endothelial progenitor cells (EPC). Hyperglycemia, obesity, hypertension and dyslipidemia have been associated with a reduction of circulating EPC. Moreover, a synergistic reduction of EPC has been associated to the clustering of metabolic disruptions (Fadini et al., 2007; Werner et al., 2005, as cited in Tiengo et al., 2008).

6. Interactions of chronic obstructive pulmonary disease, sleep apnea hypopnea syndrome and diabetes *mellitus* treatment modalities

The treatment that has shown to increase survival in COPD is smoking cessation. This is the only measure that slows the accelerated decline in lung function in these patients. COPD therapeutic approach is based on: inhaled bronchodilators, inhaled and systemic corticosteroids, pulmonary and muscular rehabilitation, anti-inflammatory drugs, oxygen and palliative symptomatic treatment in the latter stages of the disease. In a greater or lesser extent, these treatments can influence the glycemic control of DM.

To begin with, systemic corticosteroids clearly alter the metabolism of carbohydrates. Corticosteroid treatment increases upperway resistance due to fluid retention in addition to myopathy and metabolic alkalosis. In addition, corticosteroids may predispose to SAHS by promoting central obesity. Among the most widely used, methylprednisolona is the one that worsens glycemic control the most, followed by hydrocortisone. Deflazacort has less effect on diabetic control.

We can not ignore the possible effect of inhaled corticosteroids on glycemic control. Many DM patients follow an inhaled drugs schedule for their coexistent COPD. Although considered a safe treatment, some systemic effects have been described. Cataracts and suppression of the hypothalamic-pituitary-adrenal are possible effects when maximum dose are given (Faul et al., 2009). In addition, some studies have shown (Faul et al., 1998) a significant increase (1.0%) in glycated hemoglobin and the persistence of glycosuria in

patients with DM 2 who used high-dose inhaled fluticasone (2 mg / day). Other study (Slatore et al., 2009), shows that high dose of inhaled corticosteroids are associated with small changes in glycemic control that are detectable but not clinically relevant as they would not be a criteria to stop or change the treatment.

One shared mainstay of COPD and DM treatment is physical exercise. Physical activity improves lung function and provides a better tolerance of the obstructive disease. It also reduces the risk of type 2 DM (13) and improves glycemic control with a lower dose of antidiabetic agents.

Weight loss can clearly be of benefit for patients with SAHS, obesity and/or DM. Probably, a benefit can be obtained in not advanced COPD stages with excessive weight. Weight loss improves SAHS but does not cure it. In a meta-analysis about bariatric surgery and SAHS, the baseline AHI was reduced from 54.7 to 15.8 events per hour, the latter indicating a moderate to severe SAHS still remaining (Greenburg et al., 2009). Patients should be alerted that they will probably need to continue SAHS treatment after surgery. Clinicians should also be aware that weight loss is associated with increased mortality in COPD. There is no evidence to recommend weight loss in overlap syndrome.

In an indirect way, the oxygen prescribed in advanced lung disease may also influence the management of diabetes. Unfortunately we lack solid studies to verify it. The hypothesis is that control of hypoxia may improve glucose tolerance and the associated MS. CPAP treatment of SAHS has not shown to improve metabolic syndrome in obese patients (Vgontzas et al., 2008), whereas it reduces visceral fat in non obese patients (Chin et al., 1999).

As we have described how hyperglycemia may worsen COPD outcome, we could pose if diabetes treatment can improve respiratory function. Being type 2 the most prevalent DM among COPD patients, insulin sensitizers could improve the lung function. This hypothesis was tested by Kim and colleagues (Kim et al., 2010) in a retrospective cohort study. After adjustment by weight, height and glycemic control, they found an improvement of FVC in subjects treated with insulin sensitizers compared to other DM treatments, with no significant changes in FEV1 or in FEV1/FVC.

We wonder if the new anti-inflammatory drugs (anti-phosphodiesterase 4) may have an effect on control of DM trying to improve the chronic inflammation of COPD. Modulators of the oxidative process such as methyl-bardoxolona are a possibility to be explored in both chronic conditions.

7. Conclusion

We think that we should estimate the risk of diabetes in a COPD patient and *vice versa,* given the frequent simultaneity of both conditions and the confluence of common related factors.

Definitely, prospective population-based and experimental evidence is needed to elucidate the crucial pathways between chronic hypoxemic status, insulin resistance and their contributing factors, mainly tabaquism, adiposity and disordered sleep. Of note, the architecture of sleep is of growing importance in DM. Understanding the clustering of these disorders and its cardiovascular prognosis may have an epidemiological impact on the tandem increase of COPD, DM and related conditions. Probably, lifestyle interventions on tobacco, diet and sleep habits are the key to keep the individual's health and long term well-being.

8. References

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