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Elderly with COPD: comoborbitidies and systemic consequences

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Chronic obstructive pulmonary disease (COPD) represents a complex respiratory disorder characterized by persistent respiratory symptoms due to chronic airflow limitation caused by exposure to noxious particles/gases with an increased inflammatory response of the airways. COPD is common in older people, with an estimated prevalence of 10% in the US population aged > 75 years and is often accompanied by other concomitant chronic conditions that negatively impact prognosis and health status. The aim of this paper is to highlight the relationship between COPD and other comorbidities in elderly population. We focus our attention on the relationship existing between COPD and cardiovascular diseases, lung cancer, obstructive sleep apnoea syndrome, malnutrition/sarcopenia and osteoporosis with particular attention to adipokines, considering that adipose tissue plays a relevant role in the cross-talk between organs.

Key words: aging, COPD, comorbidity, adiponectin

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents a complex respiratory disorder characterized by persistent respiratory symptoms due to chronic airflow limitation caused by exposure to noxious particles/gases with an increased inflammatory response of the airways [1,2].
COPD global prevalence is about 11.7% and is responsible for around 3 million deaths annually [3]. Age is often listed as a risk factor for COPD. Chronic obstructive pulmonary disease (COPD) is common in older people, with an estimated prevalence of 10% in the US population aged > 75 years [4]. It is unclear if aging leads to COPD or if age reflects the sum of cumulative exposures throughout life [5]. COPD is often accompanied by other concomitant chronic conditions that negatively impact prognosis and health status [6,7]. A large body of literature demonstrates that comorbidities are a widespread problem in COPD patients [8-11]. A review of studies from different countries reports that 86 to 98% COPD patients have at least 1 other chronic disease with average number of comorbidities per individual ranging from 1.2 to 4.3 [9]. Furthermore, the prevalence of comorbidities was found especially high in patients with severe COPD [10]. In addition, a recent meta-analysis highlights that

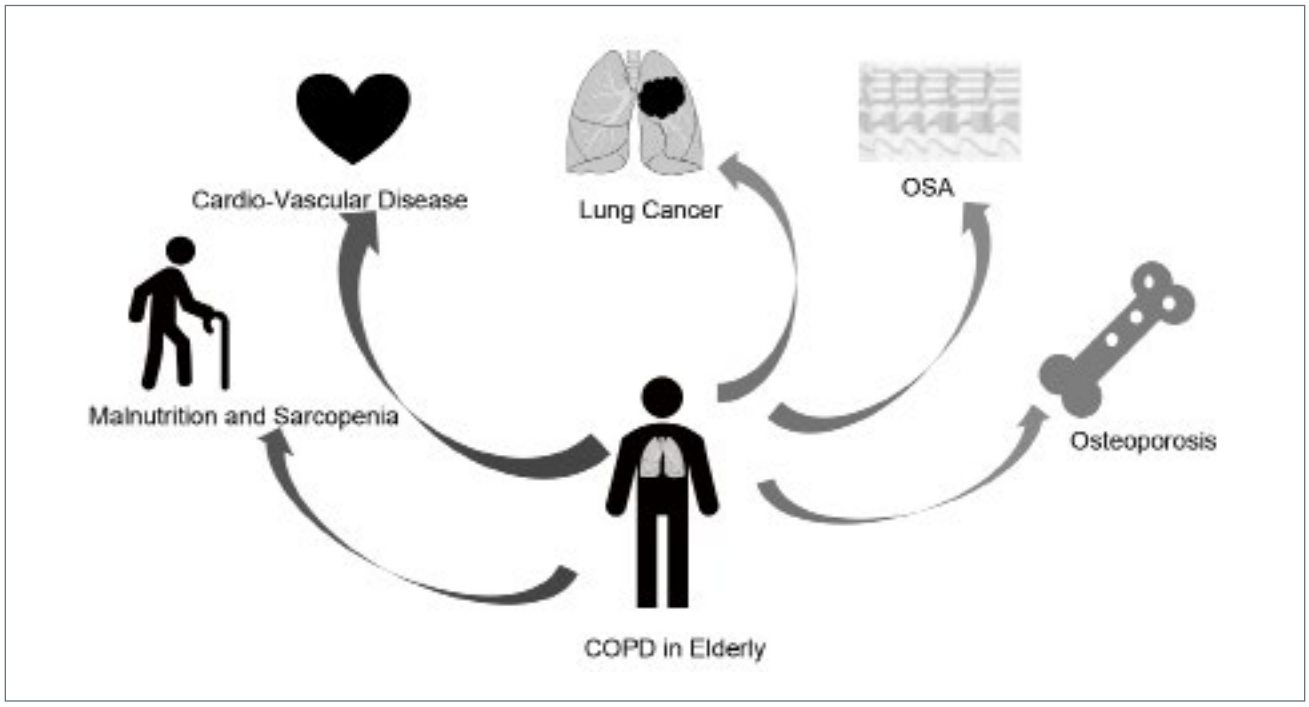

Figure 1. Chronic obstructive pulmonary disease and main comorbidites in elderly patients.

the prevalence of comorbidities in COPD patients is significantly higher in comparison to non-COPD individuals [11]. Some typical comorbidities of COPD are of particular importance for the elderly and require special attention because they are relevant for disease management in these patients [12]. Chronic systemic inflammation state in COPD may have an impact on the natural history of other chronic conditions even if its role is not totally understood [13]. Recent scientific interest has been focusing on biomolecular pathways implicated in cross-talk between organs and their potential in systemic consequences of COPD [14-18]. In this context adipose tissue appears to retain a relevant role [19].

COPD is associated with the following systemic diseases [20]:

- cardiovascular diseases: ischemic heart disease, cerebrovascular disease, peripheral artery disease, left and right heart failure, pulmonary hypertension, arrhythmias (atrial fibrillation and flutter), arterial hypertension;
- respiratory tract diseases: obstructive sleep apnea, pneumonia, lung fibrosis;
- metabolic diseases: metabolic syndrome, type II diabetes mellitus, dyslipidemia;
- haematological diseases/coagulopathies: secondary polycythemia, anaemia, venous thrombosis and pulmonary embolism;
- musculoskeletal diseases: muscle dysfunction, muscle wasting, osteoporosis;
- gastro-intestinal diseases: gastro-oesophageal reflux disease, peptic ulcer disease, liver cirrhosis;
- renal diseases: renal dysfunction;
- psychiatric diseases: depression, anxiety;
- cancers: lung, esophageal, pancreatic, breast, and all other cancers.

Comorbidities are inversely correlated with self-reported health status [9] and the presence of more than three comorbidities impacts quality of life more than lung function [21]. Moreover, the risk of exacerbation and hospitalization is related to the number of comorbidities [22], as well as the risk of mortality [23] and total annual cost of the disease [24].

Polypharmacy, defined as the use of more than 5 or 10 pharmacological agents, is another key concept in the COPD management. In the general population it is associated with multimorbidity [25] and with an increased risk of adverse drug reactions (ADRs), especially in the elderly [26-28].

Exacerbation and infectious episodes influence the course of the disease resulting in increased symptom burden [29-31].

In conclusion, in order to achieve the goal of improved quality of life and survival, the correct management of COPD in elderly should include identification and treatment of all chronic associated conditions.

In this review we discuss the relationship between COPD and other comorbidities, in elderly population.

COPD AND CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVD) are the most prevalent comorbidities in COPD elderly patients. Pulmonary hypertension, right ventricular dysfunction, arterial stiffness, systemic hypertension, left ventricular dysfunction, dysrhythmia, chronic heart failure and ischemic coronary disease have higher incidence and prevalence in patients suffering from COPD when compared with healthy population. This is not surprising because the two conditions share common risk factors, such as smoking, physical inactivity and ageing. Systemic inflammation and oxidative stress are centrally involved in the pathophysiology of both COPD and cardiovascular diseases promoting atherosclerosis [32]. The viscoelastic properties of the arteries allow propagation of the pulse wave along vessel walls generated from left ventricular ejection. The speed of this wave is directly linked to arterial stiffness. Early studies demonstrated that arterial stiffness is an independent predictor of cardiovascular accidents in other chronic pathological conditions, such as diabetes, renal failure and systemic hypertension [33]. In individuals suffering from COPD, in contrast to healthy age-matched controls, arterial stiffness has been shown to be increased, and correlates with the degree of airflow limitation. The mechanisms responsible for higher arterial stiffness in patients with COPD are largely unknown. The most plausible hypothesis is that, similar to that proposed for other chronic inflammatory condition, arterial stiffness is related to the state of chronic systemic inflammation that follows local (lung) inflammation as a consequence of "spill over" of the inflammatory process into the systemic circulation [34]. Indeed, fibrinogen levels and C-reactive protein are higher in COPD patients than in control subjects [35,36]. However, the possibility that systemic inflammation due to causative factors such as smoking exposure eventually affect the airways, thus leading to inflammatory changes that predispose to COPD, cannot be ruled out. An interesting hypothesis is that both impaired lung function and increased arterial stiffness in COPD are due to the increased susceptibility to degradation of connective tissue, as an expression of premature ageing triggered by smoking exposure. Elastolytic activity by means of metalloproteinases is enhanced in emphysema and atherosclerosis: firstly, elastin degradation leads to loss of alveolar attachments and emphysema; on the other hand, elastin degradation is associated with increased collagen and thicker arteries [37] in elderly. Hypoxia, commonly observed in advanced stages of COPD, is responsible for vasoconstriction of the pulmonary vascular bed and remodeling with myointimal hyperplasia causing, in turn, pulmonary hypertension and right ventricle hypertrophy and dilation [38]. Wats et al investigated the relationship between lung function, heart size, heart dysfunction and the consequences for 6-min walking distance (6MWD) in patients with COPD in different stages. The results of the study have shown that static hyperinflation (inspiratory-to-total lung capacity ratio [IC/TLC], functional residual capacity, and residual volume) is better related to cardiac chamber sizes than airway obstruction or diffusion capacity. The authors demonstrated that COPD patients with an IC/TLC < or = 0.25 had a significantly impaired left ventricular diastolic filling pattern and a significantly impaired global ventricular function (expressed as Tei-index) compared with patients with an IC/TLC > 0.25 [39]. Despite a clear relationship between the above-mentioned illness, results of a study from Macchia and colleagues show that at least 20% of patients with COPD suffering from left ventricular dysfunction that affects survival, are misdiagnosed [40]. For these reasons the definition of a clear protocol for diagnosis is important for management and follow up of CVD in COPD patients. André S et al. proposed a diagnostic algorithm for CVD evaluation in COPD, suggesting, in stable patients not experiencing an acute exacerbation, a baseline ECG and laboratory test such as Brain type Natriuretic Peptide (BNP) and N-terminal pro-BNP that are sensitive biomarkers of heart failure. Higher levels of BNP are associated with an increase of mortality risk. Dosing serum levels of c-reactive protein (CRP) seems to be useful also in evaluation of CVD; indeed, patients who present both moderate/severe obstruction and higher CRP serum levels have higher risk of ischemic heart disease. Echocardiogram is proposed only if needed after evaluation of symptoms and ECG [41]. Treatment of CVD in COPD patients has changed significantly in the last decade. For a long time β-blockers were not prescribed in patients with COPD fearing that their use might be responsible for bronchoconstriction. Even after the release of new molecules with higher affinity for β1 adrenergic receptors and lower for β2 receptors, COPD was still considered by a lot of clinicians a good reason for choosing another type of medication even if less effective. Several observational studies evaluated safety and efficacy of standard dose of β blockers in COPD patients, showing that their use is related to a reduction in overall mortality, exacerbation rate and severity. Furthermore, recent studies have demonstrated that β blockers could represent the best treatment of hypertension in the COPD subgroup [42]. ESC

Guidelines suggest that for patients with heart failure and concurrent COPD metoprolol, bisoprolol or nebivolol should be preferred instead of carvedilol [43].

COPD AND ADIPOKINES

Recent achievements have changed the biological view about adipocytes functions. White adipose tissue is considered an endocrine source of biologically active substances with local and/or systemic action called adipokines [44]. An inappropriate secretion of adipokines seems to participate in the pathogenesis of obesity-related diseases including endothelial dysfunction, inflammation and atherosclerosis [45]. In particular, the intercorrelation between adipose tissue and lung has become clear; the involvement of leptin and adiponectin has been demonstrated in several lung diseases such as COPD, emphysema, asthma and cancer [46-49]. In fact, through the secretion of adipokines, adipose tissue participates in the regulation of several patho-physiological processes in many organs and tissues. Among the adipokines, adiponectin and leptin are the two most relevant. The biological function of adipokines in lung diseases seems to be mainly related to the inflammatory process [50]. In fact, with specific regard to COPD, a low-grade inflammatory state has been demonstrated. Adiponectin is one of the most abundant circulating adipocytokines, accounting for the 0.01% of total serum protein. Adiponectin is involved in a wide variety of physiological processes including energy metabolism, inflammation, and vascular physiology. These effects are mediated by two atypical widely expressed seven-transmembrane receptors, AdipoR1 and AdipoR2. Adiponectin has beneficial effects in cardiovascular systems and blood vessels protecting these tissues through the inhibition of pro-inflammatory and hypertrophic responses and stimulation of endothelial cell responses. In addition, growing evidence suggests that adiponectin also exerts a crucial role on vascular endothelium maintaining vascular homoeostasis and being protective against vascular dysfunctions [51,52]. Altogether these findings support the anti-inflammatory role of adiponectin in COPD patients. Previously, we reported higher adiponectin levels in COPD compared to healthy subjects [53]. Furthermore, since adiponectin circulates as three different isoforms (low molecular weight-LMW, medium molecular weight-MMW and high molecular weight-HMW), we investigated the oligomerization state of serum adiponectin. Interestingly, we found for the first time that the adiponectin oligomerization state is altered in COPD; particularly, we observed that the higher levels of adiponectin are associated with a significant and specific increase of HMW, representing the most biologically active forms. In addition, we demonstrated the presence of AdipoR1 and AdipoR2 with a lower expression of AdipoR2 compared to AdipoR1. Moreover, we demonstrated the expression of both AdipoR1 and 2 in lung tissues from COPD with non-small cell lung cancer (NSCLC) with a lower expression of AdipoR2 compared to AdipoR1. The important role of adiponectin in patho-physiological conditions of lung is also supported by the modulation of AdipoRs with the down regulation of AdipoR2. The low expression of AdipoR2 may indicate a specific role of this receptor, mainly implicated in adiponectin effects on inflammation and oxidative stress. In addition to the above-mentioned epidemiologic studies, in vitro studies have demonstrated that adiponectin has protective effects against inflammation and the aberrant growth of cancer cells [54,55]. In particular, in a model of lung inflammation, adiponectin is able to reduce damage induced by pro-inflammatory cytokines [56]. Regarding leptin, many studies have reported that leptin provides a link between obesity and lung diseases. It is well known that leptin is a pro-inflammatory mediator in COPD disease. In fact, an increase of leptin in human sera leads to impaired immune responses and facilitates the infection resulting in increased pneumonia severity [57]. Furthermore, the upregulation of migration, inhibition of apoptosis, and increased proliferation are also found in leptin-stimulated airway epithelial cells [58]. In both in vivo and in vitro studies, leptin promoted the expression of the *cPLA2α* gene in lung alveolar type II cells via MAPK and NF-κB-activated coactivator p300 [59]. In the lung system, the increased leptin induced cPLA2α/COX-2 expression and leukocyte infiltration via the NADPH oxidase-dependent production of ROS. These evidences confirm the inflammatory effect of leptin in the lung and in particular in COPD, and suggest that leptin plays a central role in the pathogenesis of COPD in obese subjects.

COPD AND LUNG CANCER

COPD and lung cancer are closely related, based on shared main risk factors. Ongoing research is exploring the linking mechanisms, such as premature lung aging, genetic predispositions, common pathogenic factors or intracellular pathways or epigenetics factors [60].
Certainly, lung cancer is five times more common in smokers with COPD than in those with normal lung function [61,62] and COPD is an independent risk factor for lung carcinoma, mostly for squamous cell carcinoma [63]. Despite the advances in early identification and in the therapeutic management of both COPD and lung cancer the underlying networking mechanisms are far from

being well established resulting in poor prognosis [64-69].
Many epidemiological studies have showed that emphysema and air flow obstruction are both involved as risk factors for lung cancer incidence and death, but their relative roles have not been fully clarified. Firstly, both chronic respiratory obstructive diseases and lung cancer are common in the aging lung [70].
The risk of developing cancer increases with age and is higher in COPD patients over 40 years old [71,72]. Lung function decline with age is faster and premature in COPD due to oxidative stress and telomere shortening. Free radicals, such as RNOS, are exogenous (cigarettes) and also endogenous, generated by mitochondrial respiration. This is typically dysfunctional in cancer [73]. All these mechanisms lead to DNA damage, lipid peroxidation and amino acid oxidation. These evidences validate the free radical hypothesis of aging, which suggests RNOS accumulation determines DNA damage and cell transformation to malignant ones if not correctly repaired (point mutations, single and double stand breaks, DNA-crosslinking) [74].
RNOS can also inactivate tumor suppressors and apoptosis factors, allowing tumor growth to continue. RNOS are also intracellular signals activating, directly or indirectly, inflammatory and proliferative pathways (such as ROS receptor/proto-oncogene ROS1- and PI3K-mTOR pathway, c-Jun N-terminal kinases JNK, dependent mitogen activate protein kinase (MAPK), NF-Kb pathway), upregulating immune and inflammatory genes expression. Furthermore, NO stimulates tumor growth activating vascular endothelial growth factor (VEGF) [75].
Some studies have showed the correlation between short telomere length and both lung cancer and COPD [76]. Telomeres are repetitive nucleotide sequences that protect the chromosome against the shortening caused by DNA replication. When telomeres arrive at the Hayflick limit and become too short, involving the tumor suppressor proteins p53 and Retinoblastoma protein (Rb), the cell is not able to divide further and goes towards senescence. These mechanisms prevent excessive replication and the risk of generating neoplasms. However, some cells can inactivate Rb and p53 signaling pathways, giving life to a perennial clone that preserve telomere length despite cells divisions. Telomere shortening is also accelerated by smoking, leading more rapidly to replicative senescence, inflammation and emphysema, causing COPD or generating a cancer clone cell [77]. There are also evidences of a familial predisposition to lung cancer and COPD. Some regions in chromosome 6 seem to be involved: CHRNA3, CHRNA5 SNPs (15q), HHIP, FAM13A and HTR4 [78]. The rs7326277TT genotype in VEGFR1 is a locus connected with inflammation, epithelial to mesenchymal transition and tumor growth. Also epigenetic changes can be involved in the development of COPD and cancer. Hypermethylazion of tumor suppressor or gene promoters is common in lung cancer and also hypomethylation of immunomodulatory genes [79]. Methylation of the 5' position of a cytosine residue of tumor suppressor genes (*APC, CDKN2, BRCA1, RB, mdm2*) induces proliferation. A new prospective will be cluster DNA methylation patterns, corresponding to 3 lung cancer clusters and different carcinogenetic factors [80,81].
The recent EWAS study has examined the links between gene methylation in COPD and lung cancer, and the result was that methylation and repression of CCDC37 and MAP1B is associated with COPD and lung cancer [82].
Cigarette smoke reduces the activity of HDAC2 at protein and mRNA level, inducing a lower inactivation of inflammatory genes. The role of mRNAs and miRNAs is not totally clear. MiR-1 seems to be linked to cigarette smoking-related diseases and is downregulated in skeletal muscle [83]. Other miRNA involved are miR-21 and miR-146a, this one is particular because may downregulate inflammation and proliferation [84]. Considering all the common elements between COPD and lung cancer, chronic inflammation in COPD could serve as a bridge for the development of lung cancer. The inflammatory context influences the cancer microenvironment and cytokines signaling which may [85-87] interfere with therapy including Immunecheck points inhibitors [88,89]. The overexpression of NF-kB in chronic inflammation is the first mediator of inflammation-induced carcinogenesis. It induces IL-1, IL-6, IL-8, TNFα and also many factors of the cell cycle, such as cyclines D1, D2, D3, E1 and various CDKs, and suppresses p53. Cigarette smoke induces an aberrant expression of growth factors (as EGF) which increase the rate of cell division and repair lung damage. This leads to epithelial-mesenchymal transition (EMT), a process linked to both cancer and COPD. COPD patients live in a hypoxic condition (air trapping, emphysema, airflow flow obstruction) and this is a trigger to activate hypoxia inducible factor (HIF) 1-α. This factor is induced also by the cancer hypoxic environment, regulating glycolisis, telomerase activation, inhibition of apoptosis and cell differentiation. The emphysematous microenvironment could also encourage lung cancer growth. The alveolar capillary destruction and poor vascularization, typical of emphysematous areas, could lead to expression of genes of hypoxia-inducible factor-1α or could induce to mutation in genes such as TP53 and CDK2N2A. Therefore, the cells may avoid apoptosis and become able to transform into a cancerous focus. With the diffusion of computed tomography (CT), it is now possible to detect the severity of emphysema [90]. The method for evaluating emphysema

is fundamental and it appears that visual detection has a more important clinical correlation despite the automated computer analysis. The cancer results correlated only to visually-detected emphysema [91]. Contrary to common belief, several studies have noticed a possible inverse relationship between incidence of lung cancer and the severity of air flow obstruction. Older age, low BMI, DLCO < 80% predicted and GOLD Stages I and II (even small differences in FEV1 % predicted) seem to be the real independent risk factors for the development of lung cancer [92]. It is hypothesized that smokers, who develop milder disease, have a dysfunctional immune system enabling the cancer progression. Instead patients with severe COPD have a more aggressive immune system that can block cancer growth. It appears that CD4+ T-cell Th1 and Th17, CD8+ T-cell increase with the disease progression [93]. Furthermore CD8+ cells create expression of the inhibitory receptors PD1, TIM3 and PDL1 and this may explain why patients with COPD Lung cancer display longer survival with anti-PD1 antibodies [94].

Smokers with mild and moderate air flow obstruction, DLCO < 80% predicted or CT detected emphysema, have a particular risk for development of lung cancer and could represent the right target for a screening program. Lung functional parameters are also crucial in the pre-surgical evaluation of patients undergoing lung resection for lung cancer [95,96]. The United States Preventive Services Task Force (USPSTF) recommends low-dose CT since 2014 [97]. A novel score to predict lung cancer risk for patients with COPD is the COPD-LUCSS, characterized by four parameters: age > 60, BMI < 25 kg/m^2, pack-years > 60, presence of radiological emphysema; with a total range from 0 to 10 points. Low-risk patients (scores 0-6), high risk [7-10,98]. Available data show that lung cancer screening in COPD patients, using proper scores, may improve early diagnosis of lung cancer, reducing late stage diagnosis [99]. Regarding the impact on mortality, screening mild and moderate COPD significantly reduces the incidence; therefore, active screening is justified in these patients [100]. However, the benefits of a screening program are perhaps not so relevant because there are other concomitant causes of death caused by COPD [101].

COPD AND OSAS

The relationship between obstructive sleep apnoea syndrome (OSAS) and COPD has recently been a matter of great interest.

This relationship is complex, with common risk factors and hypothesized mutual causal links. Continuous positive airways pressure (CPAP) is the gold standard for the treatment of OSAS and plays a major role in the therapeutic management of the COPD-OSAS overlap syndrome. OSAS is characterized by recurrent episodes of partial or complete upper airways collapse with various respiratory events such as flow limitations, snoring, obstructive hypopneas and apnoeas. The upper airways patency – influenced by the activity of pharyngeal constrictor and dilator muscles – is therefore critical in the pathogenesis of the OSAS patients' nocturnal events. The nocturnal respiratory events and their cyclic recurrence cause oxyhaemoglobin desaturations with neurophysiological consequences like sleep fragmentation and morning sleepiness [102]. Long term negative effects on cardiac and cerebrovascular homeostasis are of great importance too. They are the reason why OSAS patients have a higher risk of arterial hypertension, arrhythmias, myocardial ischaemia and stroke [103]. In COPD patients sleep is frequently shorter and of poor quality. The cause has been traced back to the COPD itself and to pharmacologic polytherapy. During COPD patients' sleep, the ventilation physiological reduction is enhanced with a change in the ventilatory pattern and in the blood gases levels, configuring the typical pattern of the NOD (nocturnal oxygen desaturation) [104]. The suspected causative mechanisms are: reduced chemosensitivity of the respiratory nuclei, weakened contraction of the respiratory muscles, increased peripheral resistance, reduced residual functional capacity (RFC) enhanced by the supine position.The patients already hypoxemic awake, like those hypercapnic awake, show higher levels of nocturnal oxygen desaturation. Such events of oxygen desaturation are more intense during stage 3 of NREM sleep and during REM sleep [105]. For many years now the relationship between OSA and COPD is acknowledged under the title of Overlap Syndrome. About 15% of COPD patients suffer from concurrent OSA. Such patients show lower levels of nocturnal haemoglobin saturation and a higher risk of chronic cor pulmonale and arterial hypertension. Overlap syndrome patients present hypercapnia earlier when compared with COPD patients and analogue functional impairment without OSA. The therapeutic approach to the overlap syndrome consists of simultaneous treatment of both pathologies. Machado et al. observational study performed on patients suffering from COPD and OSA demonstrated a longer survival in the patients accepting CPAP as OSA treatment [106]. Marin et al. proved that the Overlap Syndrome patients had a higher risk of severe COPD exacerbation and hospitalization [107]. The discontinuation of a smoking habit and good inhaled therapy compliance are mandatory for the success of treatment. Oxygen therapy alone is not recommended in patients with COPD and OSAS especially in those with awake hypercapnia but can be of help in the

resolution of the residual desaturation after correction of the apnoeas [108]. CPAP remains the gold standard for treatment of OSA patients. BIPAP (biphasic positive airway pressure, BIPAP) is useful in patients with a low compliance to CPAP and in those with hypercapnia [109].

COPD-RELATED MALNUTRITION AND SARCOPENIA

COPD is known to negatively affect the elder patients' nutritional status, being able to produce specific morbid conditions as malnutrition and sarcopenia whose assessment is relevant for a correct management of the pathology.

Malnutrition can be diagnosed referring to the latest and widely used criteria proposed by the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2015. According to the ESPEN consensus, patients are classified as malnourished when they have a body mass index (BMI) < 18.5 kg/m^2 or between 18.5 and 22 kg/m^2, combined with a free fat mass index (FFMI) < 17 kg/m^2 for men and < 15 kg/m^2 for females. The simultaneous presence of elevated serum CRP concentrations (CRP ≥ 5 mg/dL), and/or reduced serum concentrations of albumin (albumin < 3.5 g/dL), combined with malnutrition, is a criterion for the diagnosis of cachexia or disease-related malnutrition with inflammation [110].

Sarcopenia is another nutritional phenotype to consider in the evaluation of COPD patients. Broadly accepted diagnostic criteria for sarcopenia have been developed by the European Working Group of Sarcopenia in Older People (EWGSOP), who have proposed an algorithm based on loss of skeletal muscle mass (SM) plus reduced strength and/or performance [111].

Low muscle mass can be evaluated performing a multifrequency BIA (body impedance assessment) in standardized conditions (i.e. ambient temperature between 23 and 25 °C, fast > 3 h, empty bladder, supine position for at least 10 min before starting the measurement). The skeletal muscle mass index (SMI) cut-off values are ≤ 8.50 kg/m^2 for men and ≤ 5.75 kg/m^2 for women [112].

Low muscle strength can be assessed by handgrip strength (HGS), a proxy index of overall muscle strength, measured with a digital hand-held dynamometer and expressed in kg. Patients are asked to perform a maximum voluntary isometric contraction of finger flexor muscles [113].

Physical performance is measurable by a 4-m gait speed test, as described by Kon et al. [114]. Patients are asked to walk down a 4 m flat, unobstructed course at their usual speed. Low walking speed is defined as walking slower than 0.8 m/s.

In the literature the prevalence of COPD-related malnutrition is quite variable due not only to the characteristics of patients (stages of the disease, exacerbations, etc.), but also to the use of different diagnostic approaches. De Blasio et al., using the diagnostic criteria for malnutrition proposed by the 2016 ESPEN consensus, reported an average prevalence of 19.8% [115-118] that was higher in the more advanced stages of disease, as already reported in previous papers using other diagnostic approaches [119]. The prevalence of sarcopenia, referring to EWGSOP criteria is reported to vary between the 14.5 and 25% [120]. Several factors have been shown to participate in the multifactorial aetiology of COPD-related malnutrition and sarcopenia including systemic inflammation, a well-known condition associated with COPD [121]. A recent study by Byun et al. [122] demonstrated, performing a multivariate analysis, that higher hsTNFα was a significant determinant for the presence of sarcopenia. In the same study, muscle strength assessed by HGS and muscle mass (MM) measured by skeletal muscle mass index (SMMI) showed significant correlation with levels of IL-6 and hsTNFα. Such results are noteworthy since all patients had stable, not exacerbated COPD. The notion that systemic inflammation contributes to skeletal muscle wasting in COPD patients is supported by the fact that many proinflammatory cytokines can adversely influence the skeletal muscle mass through the activation of muscle proteolysis and the inhibition of protein synthesis in elderly [123]. Experimental studies have shown that inflammatory markers, such as increased blood levels of TNF-α, promote muscle wasting by enhancing the activity of the ubiquitin proteasome pathway or by inducing apoptosis [124]. Other aetiological factors of COPD-related malnutrition and sarcopenia are: chronic hypoxia inducing a reduction in muscle mass probably as a result of the interaction of several molecular mediators such as inflammation, hypoxia inducible factor-1 signaling pathway, oxidative stress, and reduced oxidative enzyme capacity and capillary numbers; hypercapnia, which may worsen during exacerbations, negatively affecting the muscle mass through acidosis as it enhances ubiquitin-proteasome proteolytic system activity and/or through a reduction in protein anabolism; cigarette smoking; drugs, especially systemic corticosteroids; physical inactivity [125,126]. The evaluation of the nutritional status should be of primary importance in the management of COPD considering the following evidences: a low free fat mass index strongly correlates with the mortality in normal-weight COPD patients; sarcopenia is associated with loss of mobility, falls, osteoporosis, poor quality of life (QOL) due to fractures, hospitalization, and death [127].

Various therapeutic approaches have been proposed regarding COPD-related malnutrition and sarcopenia. Pulmonary rehabilitation (PR) in elderly patients with COPD

has already been proven beneficial with high-quality evidence. PR is a multidisciplinary integrated treatment program that contains exercise, education, behaviour change, and nutritional therapy. Exercise refers to a planned and repetitive activity for a specific purpose over a certain period of time, with a definition different from that of physical activity. Exercise is also one of the most effective ways to improve sarcopenia. The EWGSOP noted that exercise with a primary goal of improving physical performance, strength and muscle mass is fundamental for sarcopenia treatment [128]. Exercise in sarcopenia is largely composed of resistance exercise, aerobic exercise, and balance and flexibility exercises. Intensive resistance training by elderly patients effectively increases muscle function and mass. Nutritional support plays a key role too. Significant improvements in mid-arm muscle circumference, FFMI, 6MWT, respiratory muscle strength, and overall health-related QOL have been reported with nutritional supplementation in malnourished patients with COPD [129]. The PROT-AGE study group recommended a protein supply of 1.0 to 1.2 g/kg for healthy elderly people and 1.2 to 1.5 g/kg for elderly people with chronic or acute disease [130]. Some medicines and supplements currently available in clinical practice may be useful for patients with sarcopenia and COPD. Vitamin D is thought to play an important role in muscle metabolism, and it was recently reported that vitamin D plays a role in skeletal muscle mass and muscle strength. When vitamin D was deficient, atrophy of type II muscle fiber was confirmed. It was also reported that muscle performance was improved when the 25-hydroxy-vitamin D concentration was more than 60 nmol/L [131]. Beta-hydroxy-β-methylbutyrate (HMB) is a metabolite of leucine and is often used as a nutritional supplement during muscle training. HMB increases protein synthesis through protective and anti-catabolic effects. It also stabilizes muscle cell membranes and weakens proteolytic pathways. This process can contribute to a reduction of sarcopenia. In chronic diseases including COPD, HMB was effective in preventing muscle loss, and it was reported that the usual dose of 3 g/ day HMB was effective with no definite side effects [132,133]. Selective Androgen Receptor Modulator has recently been shown to be effective in the prevention and treatment of muscle wasting in clinical trials in cancer patients [134], and clinical trials are underway for other diseases such as COPD.

COPD AND OSTEOPOROSIS

Elderly affected by COPD experience an increased risk of developing osteoporosis. The prevalence of osteoporosis in COPD is between 4 and 59%, depending on the diagnostic method used, the population studied, and the severity of underlying respiratory disease. A recent literature survey performed in COPD patients by Graat-Verboom and colleagues showed that a number of risk factors for osteoporosis can be identified, including low body mass, disease severity, use of corticosteroids, age and female gender [135]. The presence of emphysema is a relevant factor, often associated with lower BMI and reduced BMD, and may represent a clinical phenotype at high risk of osteoporosis [136]. Another central item in patients affected by COPD is the use of systemic GCSs which play a major role in increasing bone fracture incidence and have deleterious effect on BMD. A meta-analysis made by van Staa et al. [137] showed a strong inverse correlation between bone density and total cumulative dose of GCSs. A significant correlation was also found between the daily dose of GCSs and the risk of fractures, even with low oral doses of Prednisone as 2.5 to 5 mg. In addition to this, there are several studies that demonstrated how patients receiving oral GCSs are more likely to develop one or more vertebral fractures [138]. On the other hand, the effects of inhaled corticosteroids (ICSs) on bone loss and fracture risk are less clear. Several studies reported mild effect of high doses of ICSs on bone turnover [139], moreover, a recent sub-analysis of TORCH study conducted on 658 patients revealed no significant effect of ICSs on BMD over the course of 3 years [140]. On the basis of this, the treatment of osteoporosis in patients affected by COPD aims to reduce the risk of fracture and this goal can be achieved with pharmacological and non-pharmacological intervention (such as smoking cessation and physical activity). Pharmacological interventions consist of calcium and vitamin D supplementation and anti-resorptive therapy. Tang et al. in 2007, performed a systematic review to evaluate the effects of Calcium alone or in combination with vitamin D on osteoporotic fractures and BMD in adults aged 50 years or older, stating that combination therapy is best for fracture prevention when Vitamin D alone is ineffective in preventing fractures [141]. Other drugs commonly used for the prevention and treatment of osteoporosis are bisphosphonates; several studies confirm their protective effect on bones, but few studies have specifically addressed the effect of antiresorptive agents in COPD. A randomized controlled trial performed by Smith et al demonstrated a significant improvement in lumbar spine BMD through daily intake of alendronate [142].

CONCLUSIONS

COPD is a very heterogeneous condition, common in older people. Whether aging leads to COPD or age itself reflects cumulative exposures throughout life leading to

COPD remains matter of debate. Concomitant chronic conditions are relevant and negatively impact prognosis and health status. The role of ageing on development of comorbidities in COPD is increasingly recognized and the number of comorbidities is associated to the risk of exacerbation, hospitalization and mortality in COPD. Systemic inflammation affects natural history of COPD and is implicated in concomitant chronic conditions such as cardiac failure, osteoporosis, diabetes and peripheral artery diseases. Bio-molecular pathways implicated in cross-talk between organs and their potential in systemic consequences of COPD are under investigations. Growing scientific interest has been recently focused on Adipose tissue that appears to exert a relevant role.

As COPD comorbidities in elderly are complex a multidisciplinary approach to provide a comprehensive management to a multifaceted disease is required.

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