

# Underrecognized comorbidities of chronic obstructive pulmonary disease

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**Abstract:** COPD is associated with different comorbid diseases, and their frequency increases with age. Comorbidities severely impact costs of health care, intensity of symptoms, quality of life and, most importantly, may contribute to life span shortening. Some comorbidities are well acknowledged and established in doctors' awareness. However, both everyday practice and literature searches provide evidence of other, less recognized diseases, which are frequently associated with COPD. We call them underrecognized comorbidities, and the reason why this is so may be related to their relatively low clinical significance, inefficient literature data, or data ambiguity. In this review, we describe rhinosinusitis, skin abnormalities, eye diseases, different endocrinological disorders, and gastroesophageal reflux disease. Possible links to COPD pathogenesis have been discussed, if the data were available.

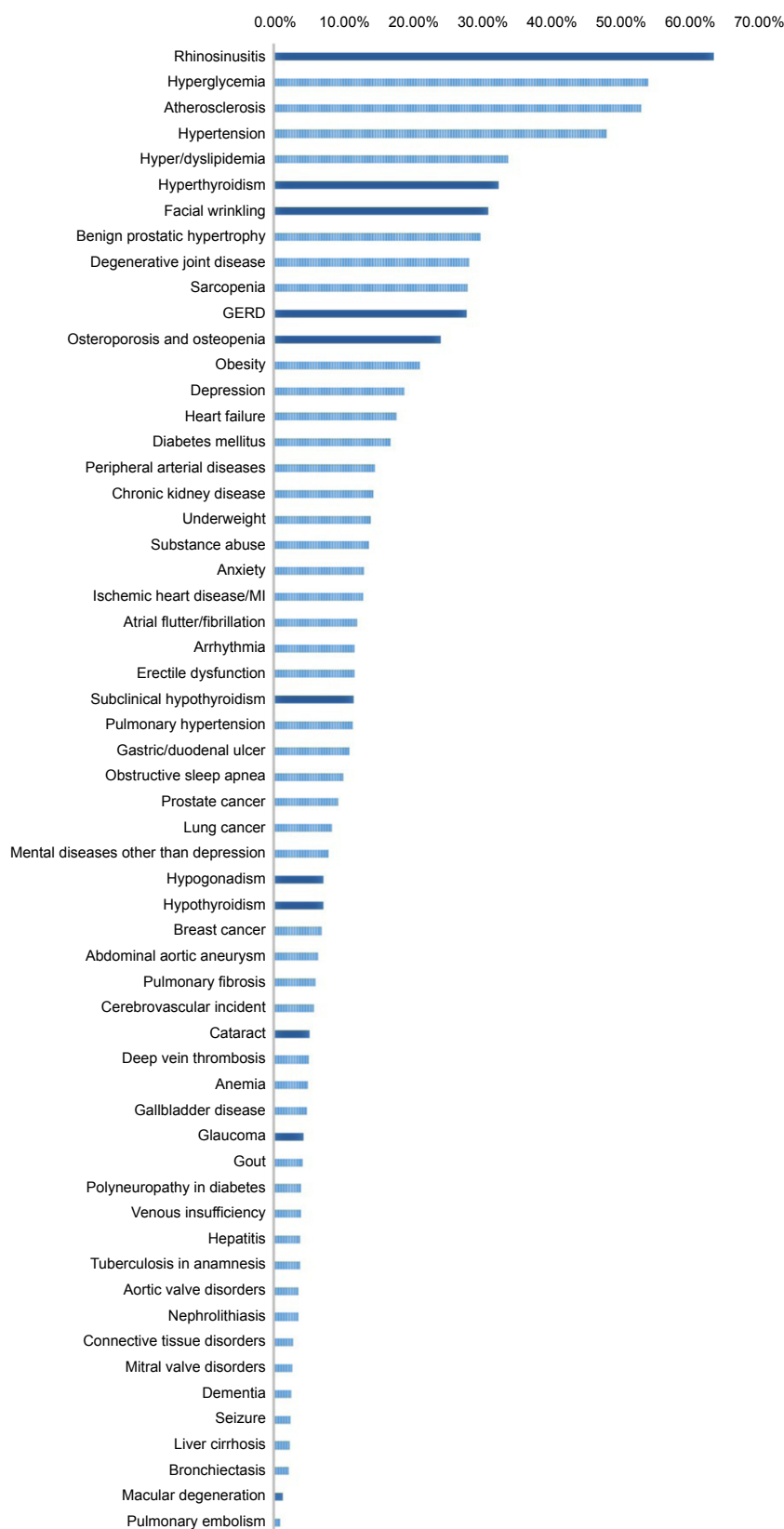
**Keywords:** COPD, comorbidities, rhinosinusitis, endocrinological disorders, GERD

## Introduction

COPD is a complex, multicomponent disease associated with pulmonary and extrapulmonary manifestations.<sup>1,2</sup> More than 30% of patients have one additional chronic disease, and another 40% have two or more comorbidities.<sup>2,3</sup> Comorbid diseases prolong hospitalization and are risk factors of short- and long-term unfavorable prognoses.<sup>4</sup> They are undeniably related to increased health care costs<sup>5,6</sup> and decreased quality of life.<sup>3,7</sup> Depression, anxiety, peripheral artery disease, cerebrovascular disease, and symptomatic heart failure have been defined as those concurrent conditions that most severely impact patients health status.<sup>8</sup> Some COPD-associated diseases are well recognized and are listed in official documents on COPD, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD). They include: cardiovascular diseases (CVDs) (ischemic heart disease, heart failure, atrial fibrillation, hypertension); osteoporosis (frequently associated with weight loss and sarcopenia); anxiety and depression; lung cancer; infections; metabolic syndrome and diabetes; bronchiectasis; and impaired cognitive function.<sup>9</sup> Figures 1 and 2 shows the prevalence of different chronic conditions, including underrecognized comorbidities discussed in this paper in patients suffering from COPD, on the basis of the available literature.

The links between COPD and other concomitant diseases are still a subject of debate. In some cases, COPD complications (like hypoxemia/hypercapnia or pulmonary hypertension) may be responsible for certain extrapulmonary symptoms. Comorbidities, like the mere index disease, may represent accelerated aging processes with shared pathological mechanisms, when chronic systemic inflammation and oxidative stress result in telomere dysfunction and DNA damage.<sup>10–13</sup> Inflammatory local response to inhaled particles and gases (mostly tobacco smoking) may spread out of the respiratory tract (the “spill-over” theory) or, alternatively, one common

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**Figure 1** The prevalence of comorbidities in COPD (prevalence >2%).

**Notes:** The diseases that are the topic of this study are marked in dark blue. Prevalence was calculated as a weighted average based on the study's sample size. When the data in a manuscript were unclear, the researchers contacted the corresponding author of the manuscript.<sup>8,18,30,31,33,39,52,62,82,83,86,89–91,95–104</sup> The calculations were performed and the graph was made in Microsoft Excel 2013.

**Abbreviations:** GERD, gastroesophageal reflux disease; MI, myocardial infarction.

trigger (like cigarette smoking) induces systemic inflammation first, and different organ manifestations result from this common root.<sup>2,10</sup> In COPD, systemic inflammation with chronic low-grade elevation of circulating proinflammatory mediators such as C-reactive protein, fibrinogen, and interleukin (IL)-6 is associated with emphysema,<sup>14</sup> accelerated disease progression characterized by acute exacerbations, COPD-related hospitalization, and rapid decline of force expiratory volume in 1 second (FEV<sub>1</sub>).<sup>15–17</sup> The same markers of systemic inflammation are also associated with aging and comorbid diseases, such as CVD, obesity, and diabetes, and are believed to actively participate in the pathogenesis of these conditions.<sup>18–20</sup> Of note, according to some studies, not all COPD patients present increased levels of inflammatory mediators in the blood. García-Aymerich et al<sup>20</sup> identified a “systemic COPD” subtype characterized by increased levels of inflammatory mediators in the blood only in a subgroup of less than one-third of the cohort. These patients were also at greater risk of having obesity, CVD, and diabetes.<sup>20</sup> Therefore, other mechanisms may be also involved in the pathogenesis of COPD and its comorbidities.

According to García-Olmos et al<sup>21</sup> COPD most frequently clusters with obesity, osteoporosis, deafness and hearing loss, malignant neoplasms, degenerative joint disease, benign prostatic hypertrophy, generalized atherosclerosis, glaucoma, chronic liver disease, dementia and delusions, chronic skin ulcer, cardiac valve disease, and Parkinson’s disease. It is worth noting that some of these diseases are not always recognized by medical professionals as frequent COPD comorbidities.

Several publications, as well as everyday clinical observations, also suggest the frequent coexistence of other conditions and manifestations, as well as involvement of organs other than those defined by GOLD.<sup>9</sup> These conditions may not be fully recognized either due to their relatively low clinical significance, inefficient literature data, or data ambiguity. Therefore, the aim of this review is to describe and discuss underrecognized extrapulmonary COPD manifestations. The term underrecognized is used in this paper to define diseases that are not listed in the updated edition of GOLD, but for which publications showing such coexistence exist. The list of exclusion and inclusion criteria is provided in Table 1. The diseases that comprise the aforementioned criteria are symptoms from the upper respiratory tract (rhinosinusitis), skin changes and accelerated aging of the skin, eye diseases, endocrine disorders (other than obesity and diabetes), and gastroesophageal reflux disease (GERD). The aim of this review is to discuss the clinical and epidemiological data on the coexistence of these diseases with COPD, as well as

**Table 1** Inclusion and exclusion criteria for underrecognized COPD comorbidities

Inclusion criteria	1. Coexistent chronic disease 2. Higher frequency compared to general population
Exclusion criteria	1. Listed in GOLD 2015 report 2. Related to treatment 3. Related exclusively to smoking habit 4. COPD complications

**Abbreviation:** GOLD, Global Initiative for Chronic Obstructive Lung Disease.

to provide (when possible) an explanation of such frequent coexistence.

## Search methodology

The initial search was conducted using PubMed with the subject headings “chronic obstructive pulmonary disease” (or “COPD”) and “comorbidities” (or “comorbidity” or “comorbidities”). Detailed headings in the area of: rhinosinusitis; skin abnormalities; eye diseases; endocrinological disorders; and gastroesophageal disease (GERD) were used. The comorbidities were selected on the basis of inclusion and exclusion criteria, as shown in Table 1. Only English articles with available abstracts were retrieved. For relevant titles, the abstracts were reviewed and, if still relevant, the full version of the article was obtained. References within the selected articles were also reviewed for their relevance. Table 2 shows the number of hits and final selection for each thematic area. The most relevant papers for this selection (showing frequent coexistence of these diseases with COPD), along with the strength of the patients cohorts, are provided in Table 3.

## Rhinosinusitis in COPD

Chronic rhinosinusitis (CRS) may be defined according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS) by presentation of symptoms and either endoscopic evidence of polyps or radiological evidence by computed tomography (CT).<sup>22</sup> These criteria may be difficult to fulfill in population-based studies. That is why in the majority of such studies, the definition of CRS is based on the sole symptoms and/or the patient’s reported physician-made diagnosis. The symptom-based diagnosis may be biased by several factors, leading to CRS overdiagnosis;<sup>23</sup> however, in the Global Allergy and Asthma European Network (GA<sup>2</sup> LEN) study,<sup>24</sup> in which 57,128 responders from 12 countries were recruited, the value of a postal questionnaire was verified against nasal endoscopy in a subgroup of over 300 patients, and symptom-based diagnosis was proved reliable. In this large study, the overall prevalence of CRS in Europe was estimated as 10.9%,

**Table 2** The process of the PubMed search in selected areas

Search area	PubMed terms	PubMed search	Abstract selection	The most relevant for the topic (number of hits)
Rhinosinusitis	COPD and rhinosinusitis	72	26	20
	COPD and sinusitis	142	52	
	COPD and rhinitis	202	84	
Skin abnormalities	COPD and skin	338	49	15
	COPD and skin pathology	71	49	
	COPD and skin aging	18	15	
Endocrinological disorders	COPD and endocrinology	75	9	17
	COPD and thyroid	136	5	
	COPD and hypogonadism	37	5	
	COPD and adrenal disorders	66	12	
Eye disorders	COPD and parathyroid	24	3	7
	COPD and eye disorders	251	34	
	COPD and eye disease	299	31	
	COPD and glaucoma	55	8	
	COPD and cataract	49	11	
	COPD and myopia	1	1	
	COPD and retina	9	4	
	COPD and age-related macular degeneration	10	5	
GERD	COPD and GERD	194	80	5

**Abbreviation:** GERD, gastroesophageal reflux disease.

and it was more common in smokers (odds ratio [OR]=1.7). The age group found to be at the highest risk of having CRS was 55–64 years.<sup>25</sup> CRS (both with and without nasal polyps) is more frequent in asthma (18%), atopic dermatitis (7%), inflammatory bowel disease (3.5%), autoimmune disorders (up to 5.9%), and the frequency of CRS associated with polyps was higher in the first three instances.<sup>26</sup>

The term “common airway disease” is used to describe the frequent coexistence of asthma and upper airway diseases – most frequently, allergic and nonallergic rhinosinusitis and nasal polyps. It has been estimated that approximately 90% of patients suffering from allergic asthma present with signs

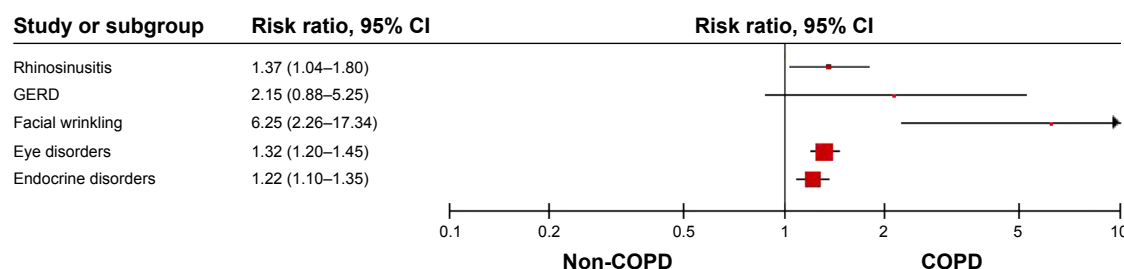
and symptoms of rhinitis, and about one-third of patients with rhinitis may have asthma.<sup>27</sup> This well-recognized association led to the formation of theories on the common pathogenesis of these concomitant diseases.<sup>28</sup>

Several authors reported on the higher incidence of CRS in COPD patients.<sup>29–33</sup> The figures depend mostly on the definition of CRS applied in a study. Upper airway symptom frequency among COPD patients may be as high as 88%,<sup>33</sup> but when more objective tests were applied for CRS diagnosis (like CT scans), lower numbers were reported (53%).<sup>31</sup> Smoking should be considered the most important risk factor of CRS. Young smokers with normal lung function present

**Table 3** List of the most relevant papers per condition

Search area	References	Year	Number of patients	COPD patients	Prevalence
Rhinosinusitis	Roberts et al <sup>30</sup>	2003	61	61	75.4%
	Piotrowska et al <sup>39</sup>	2010	63	42	97.6%
	Kelemence et al <sup>33</sup>	2011	90	90	53%
Skin abnormalities	Patel et al <sup>52</sup>	2006	149	68	31%
Endocrinological disorders	Laghi et al <sup>82</sup>	2005	101	101	38%
	Mousavi et al <sup>83</sup>	2012	140	140	58.6%
	Terzano et al <sup>94</sup>	2014	155	155	Hyperthyroidism 32.3% Hypothyroidism 21.3%
GERD	Divo et al <sup>95</sup>	2012	1,664	1,664	17.7%
	Martinez et al <sup>86</sup>	2014	4,483	4,483	29%
	Miyazaki et al <sup>89</sup>	2014	403	336	34%
	Terada et al <sup>91</sup>	2008	122	82	26.8%
	Ajmera et al <sup>90</sup>	2014	2,461	2,461	29.3%

**Abbreviation:** GERD, gastroesophageal reflux disease.



**Figure 2** Graph presents the risk ratio with the 95% CI of comorbidities, or groups of comorbidities, that constitute the topic of this study, as based on multiple studies.<sup>39,68,91</sup>

**Note:** When risk ratios were not calculated in the study, data were extracted and risk ratios were calculated.

**Abbreviations:** CI, confidence interval; GERD, gastroesophageal reflux disease.

with signs of upper airway inflammation, like increased nasal lavage cell number (the cellular pattern composed mainly of macrophages, ciliated, and goblet cells) and increased concentration of myeloperoxidase, suggestive of neutrophil recruitment and activation.<sup>34</sup> Smoking habit decreases the quality of life related to rhinosinusitis symptoms.<sup>35</sup> Smokers without evidence of pulmonary pathology also have more pathological changes in their sinus CT scans.<sup>36</sup> Many *in vitro* studies confirm the deleterious effect of cigarette smoke (CS) on nasal epithelial cells.<sup>37,38</sup> Despite these experimental studies, *in vivo* data on the role of smoking in COPD-associated rhinosinusitis are scarce. Only COPD smokers (but not the entire COPD group) were shown to have reduced mucociliary clearance and increased concentration of 8-isoprostane (a marker of oxidative stress) in nasal lavage when compared to healthy nonsmoking controls. However, no relation to smoking history and current smoking status were found for the severity of symptoms and intensity of mucosal changes.<sup>39</sup>

CRS symptoms significantly impair COPD patients' quality of life, which is usually assessed by dedicated questionnaires (Sino-Nasal Outcome Test [SNOT]-20, SNOT-22, or Sino-Nasal Assessment Questionnaire [SNAQ]-11).<sup>31–33,39</sup> However CRS symptoms do not impact the disease-specific quality of life, as scored by the use of St George's Respiratory Questionnaire, suggesting that symptoms from the lower and upper respiratory tract influence the quality of life in an independent manner.<sup>31,39</sup> The most frequently reported symptom is rhinorrhea.<sup>31</sup> Mucosal abnormalities were reported in endoscopy<sup>31,39</sup> and CT.<sup>33</sup> The symptoms were more intensive, and CT changes were more frequent in patients with more severe obstruction (grade III and IV),<sup>33</sup> but this regularity was not confirmed by other authors.<sup>39</sup> In concordance with the "common airway" concept, the most important would be to show the identity of inflammation in the lower and upper airways. Piotrowska et al<sup>39</sup> have not found any differences in the number or percentage of neutrophils, nor differences

in the concentration of LTB4 – an eicosanoid related to neutrophilic inflammation – in nasal lavages between COPD and controls. This is contrary to other authors, who found neutrophilic response in the nasal mucosa of stable COPD patients. Hurst et al<sup>40</sup> found elevated IL-8 concentrations in the nasal lavage of COPD patients, and a positive correlation with sputum IL-8. Interestingly, Hens et al<sup>32</sup> reported elevated concentrations of eotaxin (an eosinophilic marker), granulocyte colony-stimulating factor and interferon- $\gamma$  in the nasal lavage of COPD patients; moreover, the very same cytokines were found to be elevated in lavages of patients with asthma. Vachier et al<sup>41</sup> reported higher numbers of CD8<sup>+</sup> and neutrophils in the nasal biopsies of COPD patients. This is the only study so far, with the use of nasal biopsy, to prove the typical signs of COPD inflammation in the nose. No relation to systemic inflammation, defined as elevated serum C-reactive protein concentration, was found.<sup>39,40</sup>

## Skin in COPD

A typical "smokers' face" is characterized by prominent wrinkles, gauntness of facial features, gray appearance of the skin, and a swollen complexion. The association between smoking habit, its intensity, and skin wrinkling was documented many years ago.<sup>42</sup> Skin wrinkling supposedly reflects accelerated skin aging. CS induces low-grade skin inflammation mediated by reactive oxygen species, which leads to alterations in extracellular matrix turnover. Collagen I and collagen III content in smokers' skin is decreased, which may result from decreased collagen biosynthesis and/or increased degradation. Increased expression of matrix metalloproteinases ([MMP]-1, MMP-2, MMP-3, MMP-7, and MMP-8) and decreased expression of tissue inhibitor of metalloproteinases-1 have been reported.<sup>43–47</sup> The skin inflammation induced by smoking may resemble that related to chronic exposure to solar ultraviolet radiation – also referred to as photodamage or photoaging. This type of



damage is associated with skin infiltration with mast cells, macrophages, CD4<sup>+</sup>CD45RO<sup>+</sup> T-cells, and CD1a<sup>+</sup> dendritic cells.<sup>48–50</sup> It was shown, that smoking accelerates skin photoaging, whereas smoking cessation may slow down this process.<sup>51</sup>

The skin of COPD patients also shows signs of accelerated aging, but only in those parts related to the smoking habit. Patel et al<sup>52</sup> were the first to prove the susceptibility of smokers with facial wrinkling to COPD. According to these authors, facial wrinkling was not only related to COPD risk (OR = 5.0), but its intensity also correlated with the extent of emphysema on CT scans. Other authors have shown that COPD patients have increased skin elastin degradation when compared to smoking-matched control subjects. It was more pronounced in the areas exposed to solar radiation when compared to areas protected from the sun. Of much interest, the intensity of elastin degradation in skin biopsies was correlated with emphysema severity, as assessed by chest CT, and it was shown to be related to messenger RNA expression of MMP-2 and MMP-9.<sup>53</sup> This finding is aligned with the results of another group of authors, who found an association between elastin fiber abnormalities in the reticular dermis and lung function impairment of an obstructive pattern.<sup>54</sup> However, skin fibroblasts do not show the same “senescent” as the emphysema-derived pulmonary fibroblast phenotype.<sup>55</sup>

Advanced glycation end products (AGE) are generated by the glycation and oxidation of proteins. AGE accumulate in the tissues and thus may impair the function of different organs. Moreover, when attached to cellular receptors (RAGE), they induce a cascade of events leading to the activation of nuclear factor kappa B, which result in the generation of proinflammatory cytokines. AGE and RAGE have been associated with the pathogenesis of many diseases with underlying systemic inflammation, such as diabetes, heart insufficiency, chronic kidney disease and, recently, COPD.<sup>56–58</sup> Serum AGE and cellular RAGE expression were both elevated in COPD,<sup>59</sup> and sRAGE, a circulating soluble decoy receptor, was shown to be decreased in COPD, which was inversely correlated with the degree of emphysema.<sup>60</sup> The skin of COPD patients accumulate AGE, which can be detected by skin autofluorescence.<sup>61,62</sup> In none of these studies does skin autofluorescence intensity correlate with COPD severity.

## Eyes in COPD

Hypoxia and vascular mediators may be involved in the etiology of some eye disorders. A constant supply of oxygen is

crucial to maintain adequate organ function – in particular, in tissues with high energy demand, such as the retina. Thus, it does not come as a surprise that even small alterations in retinal oxygen tension may lead to tissue hypoxia and neuronal death.<sup>63</sup> New instruments allow for the noninvasive measurement of retinal oxygen saturation in humans.<sup>63</sup> Celik et al<sup>64</sup> evaluated the hemodynamic changes in the extraocular orbital vessels of COPD using color Doppler ultrasonography and showed that severe (stage 3) COPD is associated with impaired retrobulbar hemodynamics.

Glaucoma and cataract may be assigned to side effects of COPD treatment. Topical and systemic corticosteroids are well known to raise intraocular pressure, while the effect of inhaled corticosteroids on the risk of glaucoma remains uncertain. In a large cohort of elderly patients treated for airways disease, neither current nor continuous use of high-dose inhaled corticosteroids resulted in an increased risk of glaucoma or raised intraocular pressure requiring treatment.<sup>65</sup> COPD, like glaucoma and cataract, is a common disease in the elderly. In those individuals above the age of 70 years, glaucoma prevalence is close to 4%.<sup>66</sup> A population-based cohort study with nested case–control analysis using the United Kingdom General Practice Research Database did not find an association between glaucoma and obstructive airway diseases.<sup>67</sup> Quite the contrary, Soriano et al<sup>68</sup> in a large cohort of COPD patients (number [n] = 2,699) from the same database, found that COPD compared to non-COPD patients are at higher risk of glaucoma within the first year after COPD diagnosis (risk ratio [RR] = 1.3). Of note, 2% of COPD patients had a record of their cataracts, but this rate was not different than that of the non-COPD cohort.<sup>68</sup>

It was also shown that individuals with neovascular age-related macular degeneration are significantly more likely to have emphysema and COPD. Also, hypertension, hypercholesterolemia, atherosclerosis, arthritis, coronary heart disease, cataract, glaucoma, and myopia were found to be more frequent in these patients.<sup>69</sup> Independently of smoking, a history of emphysema, respiratory symptoms, and lung function impairment are modestly, but inconsistently, associated with the incidence and progression of age-related macular degeneration.<sup>70</sup>

Significant decreases in endothelial cell density, hexagonality, corneal thickness, and a significant increase in the endothelial cell size coefficient of variation were found in COPD patients. They also presented with a significant decrease in serum antioxidant enzyme paraoxonase (PON)1 activity, but not in PON1 concentration. Serum PON1 activity

showed a significant direct association with endothelial cell density and an inverse association with corneal thickness. Therefore, the authors suggest that PON1 may be involved in the pathophysiology of corneal endothelial alterations in patients with COPD.<sup>71</sup>

## Endocrinological disorders in COPD patients

Diabetes mellitus type 2, osteoporosis, and metabolic syndrome are well-known endocrinological comorbidities in COPD.<sup>9</sup> In some patients, COPD is associated with muscle wasting and weakness, and thus many reports are focused on anabolic hormones, thyroid function, and the adrenal glands.<sup>72</sup> A range of mechanisms, including systemic inflammation, neurohormones, blood gas disturbances, and glucocorticoid administration, contribute to the anabolic/catabolic imbalance and impaired whole-body metabolism in COPD.<sup>73–76</sup>

Some studies show that thyroid diseases are more frequent among patients with COPD. In a big population-based study performed in the city of Madrid, Spain, it was shown that the prevalence of a thyroid disease was higher in COPD patients (14.21%) than the expected standardized prevalence of chronic diseases (11.06%).<sup>21</sup> A strong positive correlation between the total T3/total T4 ratio and PaO<sub>2</sub> in patients with respiratory insufficiency was described.<sup>75</sup> Increased free (F)T3 concentrations have been reported in stable COPD, with a positive association to PaCO<sub>2</sub>,<sup>76</sup> while others reported lower total T3, FT3, and totalT3/totalT4 ratios in patients with severe hypoxemia.<sup>77</sup> Mancini et al<sup>78</sup> evaluated thyroid hormones and antioxidant defense – the lipophilic coenzyme Q10 (CoQ<sub>10</sub>) and total antioxidant capacity – in COPD patients to reveal the presence of a low-T3 syndrome in COPD and to investigate the correlation between thyroid hormones, lung function parameters, and antioxidants. They found significantly lower FT3 and FT4 levels and significantly higher thyroid-stimulating hormone levels in COPD patients versus controls.<sup>78</sup> Their research seems to indicate an increased oxidative stress in low FT3 COPD and a role of FT3 in modulating antioxidant defense. These data might suggest the need for thyroid replacement therapy in a low-T3 syndrome in COPD patients.<sup>78</sup>

Many studies have shown that middle-aged and elderly COPD patients may develop hypogonadism.<sup>79–82</sup> The prevalence of hypogonadism in men with COPD can range from 22%–69%, and it has been associated with several other systemic manifestations including osteoporosis, depression, and muscle weakness.<sup>79</sup> However, the relationship between

hypogonadism and COPD still remains poorly understood. The current literature is, at best, circumstantial.<sup>79,82</sup> A sex hormone deficiency in men can be correlated with COPD stages and disease progression.<sup>83</sup> There are only a few long-term trials evaluating the effects of androgens on the parameters of respiratory function in patients with COPD.<sup>79,83,84</sup> Changes of testosterone levels in patients with COPD correlate with FEV<sub>1</sub>, hypoxemia, and hypercapnia levels.<sup>79,84</sup> Glucocorticosteroids exacerbate androgen deficiency in patients with COPD, and the use of hormone replacement therapy with testosterone in these patients is justified. Androgens, especially the testosterone depot, can be effectively used in the treatment and rehabilitation of patients with COPD.<sup>85</sup> Testosterone replacement therapy may result in modest improvements in fat-free mass and limb muscle strength, but its therapeutic efficacy in COPD patients still remains controversial.<sup>79</sup>

Adrenal insufficiency (AI) is an uncommon but life-threatening disorder if it progresses to adrenal crisis. In some COPD patients, previous glucocorticosteroid intake may be responsible for the occurrence of AI. The annual incidence of AI in Taiwan has continuously increased in recent years, and elderly patients accounted for the majority of the increase. The most common comorbidity for AI was pneumonia (6.4%), followed by urinary tract infection (6.4%), diabetes mellitus (6.2%), electrolyte imbalance (4.8%), and COPD (4.5%).<sup>85</sup>

It has been suggested that COPD patients have abnormal circadian rhythms, and they suffer from cognitive function, mood/anxiety, and sleep abnormalities because of disturbances in corticosterone release – an adrenal steroid that plays a considerable role in stress and anti-inflammatory responses.<sup>74</sup>

## Gastroesophageal reflux disease

The frequent coexistence of GERD among patients with COPD has been described before.<sup>86</sup> Treatment with bronchodilators (such as theophylline or beta-agonists) has been considered as causative factors; however, the literature data on the possible causative links are ambiguous.<sup>87</sup> Obstructive sleep apnea, a frequent comorbidity of COPD, may also exacerbate diaphragm and lower esophageal sphincter dysfunction and increase the propensity for and severity of GERD.<sup>88</sup> It may not be excluded that mere COPD symptoms (like frequent and severe cough) increase the intrathoracic pressure, thus contributing to reflux occurrence; however, the data confirming this hypothesis are lacking. GERD was present in almost one-third of elderly COPD patients and

it shows female predominance.<sup>89</sup> It was shown to be associated with a higher risk of cardiovascular comorbidity.<sup>90</sup> It significantly impacts the severity of symptoms<sup>89,90</sup> and quality of life.<sup>89,90</sup> Coexistent GERD significantly increases health care costs.<sup>90</sup> GERD symptoms were also shown to be associated with a higher risk of exacerbations (RR =6.5).<sup>91</sup> The presence of GERD symptoms does not influence the inflammatory response in the airways;<sup>92</sup> therefore, other mechanisms by which GERD affects COPD exacerbations should be sought. The increase in bronchial hyperresponsiveness in patients with GERD could explain the impact on COPD symptoms and the increased risk of exacerbations; however, it was shown that the treatment of patients with severe hyperresponsiveness (both asthma and COPD) and coexisting GERD with a high-dose proton pump inhibitor for a period of 3 months did not alleviate respiratory symptoms, nor did it decrease the threshold of bronchial hyperreactivity.<sup>92</sup>

## Other underrecognized manifestations

Little was known about the relationships between COPD and liver diseases until population-based surveys demonstrated that COPD patients have a substantially elevated risk of gallbladder disease, pancreatic disease, and asymptomatic elevations of hepatic transaminases unrelated to right heart failure.<sup>93</sup> The same survey and retrospective study revealed that renal complications of COPD are common, especially among patients with hypoxemia and hypercarbia. Renal–endocrine mechanisms, tissue hypoxia, and vascular rigidity play roles in the pathophysiology, but a causal relationship is not precisely recognized.<sup>93</sup>

## Conclusion

Not all is known about COPD comorbidities. Many symptoms may be overlooked or belittled by physicians. Sometimes it is difficult to distinguish between COPD complications, drug-related symptoms and treatment complications, and real comorbidities. Quality of life is one of the main indications of well-being and it may be severely impaired by still underrecognized manifestations. Some of these comorbidities may even be life threatening. Common pathways may be involved in the pathogenesis of COPD and its comorbidities. Therefore, better recognition of these complicated relationships between different diseases may be important for the knowledge on the COPD itself. Improved management of these conditions may result in improved quality of life and health care-related cost reduction.

## Acknowledgment

The authors are supported by the Healthy Ageing Research Centre project (REGPOT-2012-2013-1, 7FP).

## Disclosure

The authors report no conflicts of interest in this work.

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