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Navigating The Complex Landscape Of COPD And Comorbidities: Impact, Mechanisms, And Management

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Abstract:

COPD is a major global health issue, with an increasing morbidity and mortality rate. By 2020, it was estimated to result in over 6 million deaths annually. COPD is associated with various comorbidities, including chronic heart failure, hypertension, diabetes, osteoporosis, and more. Smoking, the primary risk factor for COPD, is also a major contributor to these comorbidities. Smoking not only affects the lungs but also various other organs, leading to cardiovascular complications and other chronic conditions in COPD patients. The number of comorbidities in COPD patients is associated with increased hospital deaths, and these conditions significantly affect the quality of life. Highly prevalent comorbidities, such as heart failure and diabetes, are linked to a decrease in the quality-of-life scores. Traditional lung function tests, like FEV1, inadequately correlate with COPD symptoms and comorbidities. Therefore, new multidimensional indices have been developed to better assess COPD and its comorbidities. The article explores various mechanisms underlying COPD and its comorbidities, including smoking, hypoxia, inflammation, endothelial dysfunction, platelet reactivity, arterial stiffness, and coronary artery disease. The management of COPD and its comorbidities involves long-term oxygen therapy and pharmacologic treatments. Oxygen therapy not only reduces mortality but also improves various aspects of patient health. Corticosteroid treatment approach Leads to multiple chronic disease conditions so alternate drug regimen. The effects of pharmacologic treatments on COPD mortality remain a subject of research. The article concludes by emphasizing the need for a comprehensive and multidisciplinary approach to managing COPD and its comorbidities.

Keywords: **Morbidity, Smoking, COPD, Comorbidities, Oxygen therapy, Mortality.**

Introduction:

Chronic Diseases are the biggest arising problem to global health, with two of every three deaths around the world attributed to non-communicable diseases. Alarmingly, Chronic obstructive pulmonary disease (COPD) is now the third leading cause of death in the world. Although COPD primarily affects the lungs, it is now also recognised as a complex multi-component complaint characterized by chronic systemic inflammation that constantly coexists with other conditions known as comorbidities. Comorbidities in COPD are common at any stage of the complaint(1).

According to some study, the morbidity and mortality rate of chronic obstructive pulmonary disease (COPD) is continuously rising. By 2020, COPD is may result in over 6 million deaths annually worldwide, therefore getting the third leading cause of death in the world. The general ageing of the world's population is buttressing this

trend, incompletely since the chances is greater in age groups >50 years (the average age of cases with COPD is 70 years), and incompletely because incidence remains high in the old people. For a male aged >55 years who's free from COPD, the estimated threat of developing COPD over the coming 40 years is 24%(2,3)

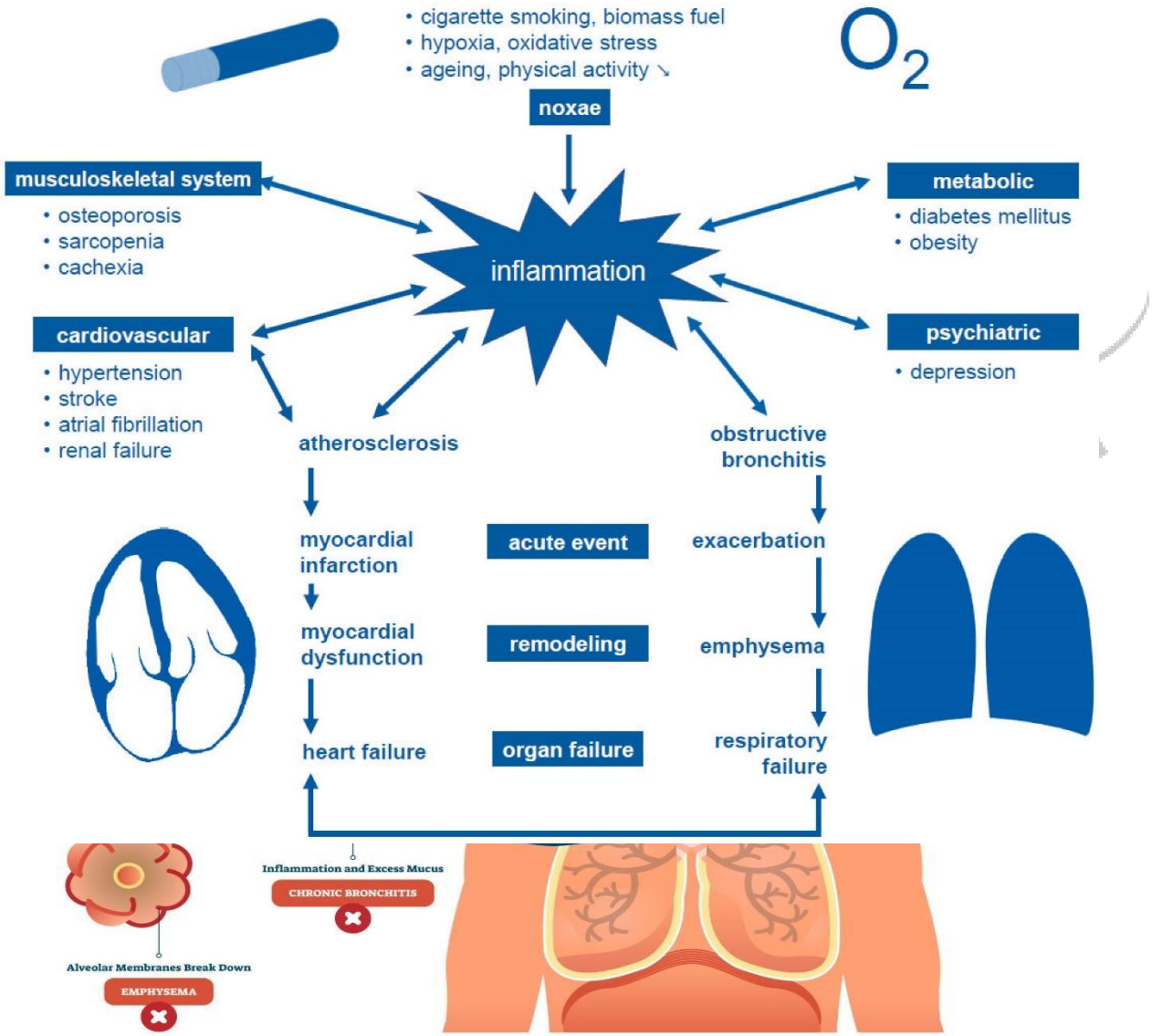
COPD and it's common comorbidities

COPD (chronic obstructive pulmonary disease) is a group of lung diseases that make it hard to breathe and get worse over time. Emphysema affects the air sacs in lungs, as well as the walls between them. They become damaged and are less elastic. Chronic bronchitis, in which the lining of airways is constantly irritated and inflamed. This causes the lining to swell and make mucus. spirometric assessment inadequately correlates with the sign and symptoms of COPD, and a large proportion of smokers with habitual respiratory symptoms do not meet the spirometric criteria. Cigarette smoking, the most important and best- established responsible factor for COPD, is also a major threat for all other chronic conditions and cancer, not only because it damages the lung directly, but also because it may affect all organs simultaneously. The most common comorbidities of COPD that are conceivably affiliated to the systemic effects of smoking are CHF, arrhythmias, hypertension, cachexia, skeletal muscle abnormalities, and infections, peripheral and coronary artery diseases, diabetes and metabolic syndrome, osteoporosis, cancer (particularly lung cancer), pulmonary vascular abnormalities, psychiatric disorders(4–6).

Therefore, the systemic effects of smoking may significantly contribute not only to the respiratory abnormalities, symptoms, and functional impairment associated with COPD, but also to the clinical respiratory and nonrespiratory clinical manifestations related to the chronic conditions frequently associated with COPD. Low- grade systemic inflammation caused by smoking and other risk factors has also been intertwined in the pathogenesis of cardiovascular events and chronic myopathy of the skeletal muscle; since people with COPD suffer from excess morbidity and mortality related to cardiovascular events, it has been suggested that systemic inflammation may be the common link. COPD is an independent risk factor for cardiovascular diseases. Arterial wall stiffness, which relates to cardiovascular threat, is increased in people with COPD compared with control subjects who smoke. This suggests that COPD may affect in systemic endothelial dysfunction, which may be a medium for the enhanced cardiovascular threat in COPD. Systemic arterial wall stiffness is also singly related to emphysema as assessed by CT scanning and correlates with osteoporosis, another systemic complication of COPD. These studies raise the interesting possibility that mechanisms that affect in alveolar wall destruction and emphysema may also produce increased cardiovascular threat and osteoporosis in cases with COPD. Comorbidities are largely likely to affect health issues in COPD, and cases with COPD are more likely to die of cardiovascular complications or cancer than of respiratory failure. Progressive respiratory failure accounts for roughly one third of COPD-related deaths; thus, factors other than the progression of lung diseases must play a substantial role(7).

The number of pre-existing comorbidities in people with COPD is associated with increased in hospital deaths. Co-morbid conditions that have been associated with an increased mortality threat in people with COPD include chronic renal failure, and pulmonary vascular disease. Underlying heart conditions haven't been constantly associated with a advanced mortality risk. Still, because COPD is constantly underreported, it is difficult to make an accurate estimate of how co-morbid conditions influence COPD mortality or, conversely, how COPD affects the outgrowth of other diagnosis. In addition to smoking, the other major responsible factor for cardiovascular and other chronic co-morbid conditions is obesity. Although obesity by itself may affect lung function, its relationship with COPD has been inadequately investigated and is still unclear. However, obesity is responsible for affecting respiratory system in several ways. Multiple cross-sectional studies have demonstrated an inverse relationship between FEV1 and body mass index (lung. This is of particular significance because FEV1 is an independent predictor of all-cause mortality and a strong risk factor for cardiovascular disease, stroke, and lung cancer. Thus, considering the frequent comorbidities, the concept of COPD as a disease diagnosed and monitored with lung function (e.g., FEV1) is getting outdated and likely compromises patient care. It is suggested that patients would benefit from an earlier, broad-based, and aggressive approach to management(4,8,9)

Comorbidities With COPD



Comorbidities impact on quality of life:

Quality of life and self-reported health status decrease with an adding number of comorbidities in cases with, 14,15 van Manen et al14 demonstrated that three or further comorbidities more identified with health- related quality of life scores than forced expiratory volume in 1 second (FEV1) or dyspnea. Putcha et al2 investigated the impact of comorbidities on self-reported health status in 41,658 patients as part of the National Health and Nutrition Examination Survey (NHANES) survey between 2001 and 2008. For every fresh comorbidity, the odds of poorer self-rated health were increased by 43%. Highly prevalent comorbidities such as heart failure, diabetes, arthritis, and urinary incontinence/prostatic disease were individually associated with a significant decrease in quality-of-life score, adjusted for age, sex, race, and other comorbidities(10).

Measurement and assessment of comorbidities in COPD:

The complexities and frequent comorbidities of COPD necessitate assessment beyond airflow limitation (forced expiratory volume in 1 s—FEV1).70 Of interest, the notion that the volume of air exhaled from a completely inflated lung could be an important indicator of unseasonable death dates back to the mid-19th century.71 Interestingly enough, when it was first put forward, the dimension was used in the insurance assiduity to identify people who were at threat of dying prematurely.72 Much has evolved over the years and it is now recognized that FEV1 is poorly related to the severity of breathlessness, exercise limitation, health status impairment and the extra pulmonary dimensions of COPD. Henceforth, other multidimensional indices are now being used for prognostic purposes over the last many times there have been numerous new publications that propose, validate, and recommend new multi-dimensional indices for the assessment, management or prognostication of COPD and its comorbidities. Some have been developed specifically for comorbidities, such as the Comorbidity Index (CCI), comorbidity test (COTE index), CODEx index (comorbidity, airway Obstruction, dyspnoea and previous exacerbation),COMCOLD index (comorbidities in chronic obstructive lung disease) and DECAF score (dyspnoea, Eosinopenia, consolidation, acidaemia and atrial Fibrillation)(11,12). Others were developed to provide a Multi-dimensional approach to assessing COPD, Excluding co-morbidities (e.g. BODE index (body mass Index, airflow obstruction , dyspnoea and exercise Capacity), modified BODE indices (mBODE, e-BODE, BODEx), ADO (age, dyspnoea and air flow obstruction), DOSE (dyspnoea, airflow obstruction, smoking Status and exacerbation) and GOLD (Global Initiative For Chronic Obstructive Lung Disease) quadrant)(1)

Table 1 – The assessment of comorbidities in COPD.

Mode of assessment	Description	The spectrum of comorbidities
Charlson comorbidity index	A standard scale with 15 chronic diseases graded for severity of disease	Myocardial infarction, HF, peripheral artery disease, cerebrovascular disease, dementia, diabetes, liver disease, peptic ulcer disease etc.
COTE index	A quantitative risk stratification comorbidity tool which is based on 12 comorbidities that influence survival in COPD	Oncologic (lung, pancreatic, esophageal, and breast cancers) Pulmonary (pulmonary fibrosis) Cardiac (atrial fibrillation/flutter, congestive heart failure, and coronary artery disease) Gastrointestinal (gastric/ duodenal ulcer, liver cirrhosis) Endocrine (diabetes with neuropathy) Psychiatric (anxiety)
Comorbidity, airway Obstruction, Dyspnea, and previous Exacerbation (CODEx) index	A prognostic tool to assess mortality, hospital readmission and their composite impact for 3–12 months after hospital discharge in patients hospitalized for exacerbation of COPD	Comorbidity is measured using the age-adjusted Charlson index. Dyspnea, obstruction, and severe exacerbations are calculated according to BODEX (BMI, airflow obstruction, dyspnea, and previous severe exacerbations) thresholds
Comorbidities in Chronic Obstructive Lung Disease (COMCOLD) index	Five comorbidities with greatest impact on patient-reported health status	Depression, anxiety, peripheral artery disease, cerebrovascular disease and symptomatic heart disease
DECAF score	The five strongest predictors of mortality in patients with COPD exacerbation and pneumonia	Extended MRC Dyspnea Score, eosinopenia, consolidation, acidaemia, and atrial fibrillation
COPDCoRi	An algorithm for predicting the risk of CAD in COPD patients	CAD
Comorbidome	A graphical expression of the comorbidity prevalence and risk of death in the form of an orbital bubble chart	The same as for COTE index

Mechanisms of COPD:

Despite the substantiation of frequent clinical association, the underlying common biological and pathological mechanisms remain still largely unexplored.

▪ Smoking habit.

It's well known that cigarette smoking plays a commanding part for the development of both COPD and IHD. Smoke and other inhaled noxious patches similar as biomass energies or gases are the crucial factors in lung and arterial wall inflammatory response. This patient seditious response induces Chronic airways obstruction, promotes atherosclerosis, and favours coronary plaque instability(1,13,14)

▪ Hypoxia, inflammation, and endothelial dysfunction(15).

Local (airways and vessels) and systemic inflammation and hypoxia are constantly and simultaneously present in COPD and IHD. Hypoxia is responsible of the activation of renin-angiotensin system, inducing peripheral vasoconstriction and reducing renal blood flow, and may lead to oxidative stress and myocardial infarction. COPD cases showed patient systemic inflammation and increased situations of acute phase proteins as interleukin- 6(IL- 6), C- reactive protein (CRP) and fibrinogen. Fibrinogen is involved in the atherosclerotic process, converting shrine growing, stimulating the adhesion of platelets and white blood cells to the vessels wall and promoting muscle cell proliferation and migration. High plasmatic levels of fibrinogen are directly related to risk of ACS. CRP is an acute phase protein released after vascular damage, it Stimulates the production of IL-6 and endothelin-1 and it is well related to cardiovascular outcome in patients with and without IHD . IL-6 may lead to atherosclerotic plaque formation(16–18).

▪ Platelet reactivity.

COPD- related systemic inflammatory status may significantly affect also platelet reactivity(PR) and responsiveness to antiplatelet drugs. Indeed, as a result of inflammation, COPD patients have decreased platelet volume and increased platelet count . High on-treatment PR is a strong predictor of poor prognosis in patients undergoing PCI and stent implantation. Recently, we showed that on-treatment PR is significantly higher in COPD patients . This finding is independent to age, sex, cardiovascular risk factors and clinical presentation of IHD . In COPD patients on dual antiplatelet therapy (aspirin + clopidogrel), we observed a lower drug responsiveness compared to patients without COPD . The recently reported survival enhancement of COPD cases after antiplatelet medicine administration, may be considered a further(19,20).

▪ Arterial stiffness

COPD is explosively related to increased arterial stiffness , because of several factors increased blood pressure(systolic and diastolic), inflexibility of inflammation, increased coronary roadway calcium, aged age, imbalance between protease and anti-protease, inflexibility of hypoxia, habitual hyperglycaemia . Also, matrix metalloproteinase(MMP)- 2, MMP- 9 and neutrophil elastase increase in COPD cases . These proteases are intertwined in a multitude of pathological processes, as atherosclerotic shrine conformation, destabilization and rupture, thrombus conformation , and change of the arrangement of wall vessel elastic filaments. Several studies showed a strong relationship between arterial stiffness and GOLD stage of COPD. Cases in the GOLD stage III/ IV showed a significantly advanced arterial stiffness, which is an independent predictor of cardiovascular events and mortality(21,22).

▪ Extension of coronary artery disease.

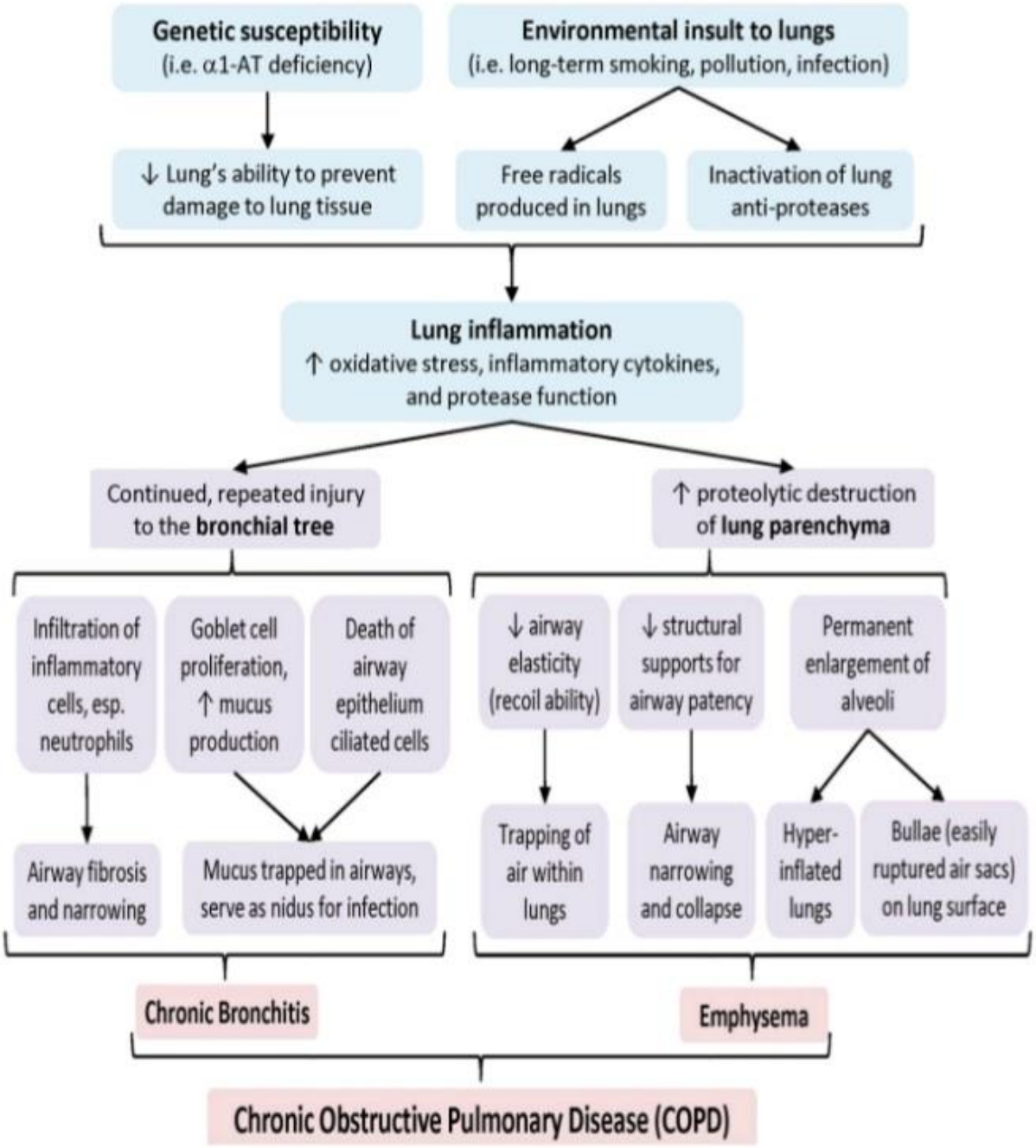
Primary angiographic studies showed worse atherosclerotic burden and atherosclerotic lesion parcels in cases with COPD as compared to those without. Particularly, coronary roadway calcifications are more severe in COPD cases. Interestingly, in these cases a high Agaston score (circular indicator of coronary calcium) is prophetic for mortality.

▪ Right ventricle morphology and function.

A recent study of Hilde etal. Showed the presence of original signs of right ventricle redoing mild hypertrophy, dilatation or reduced systolic function) in COPD cases, indeed with normal pulmonary roadway systolic pressure. These findings suggested that COPD pathophysiological mechanisms induce an unseasonable damage on right ventricle(23,24)

• Abnormalities in coagulation Cascade.

Studies on thrombin generation profile of COPD cases compared to healthy subjects, showed increased situations of prothrombin, coagulation factors II, V, VII, VIII and IX and lower position of free towel factor pathway asset. Therefore, advanced maximum thrombin situations, rates of thrombin generation and total thrombin conformation are observed. These findings may contribute to the altered thrombotic phenotype of COPD cases(25,26)



Management approaches:

Supplemental oxygen therapy

Long-term supplemental oxygen therapy reduces mortality from All causes in patients with hypoxemic COPD, but whether It specifically reduces cardiovascular, respiratory, metabolic, or Cancer mortality is not known. However, in addition to its effect on mortality, long- term oxygen remedy reduces dyspnea, polycythemia, pulmonary artery pressures, sleep disorders, nocturnal Arrhythmias, and neuropsychiatric abnormalities and improves Exercise tolerance, suggesting that its effects go far beyond the lungs. An intriguing model comes from the substantiation that oxygen remedy improves renal function in cases with COPD.(27,28)

Pharmacologic Treatment

The first and only COPD randomized clinical trial to address the effect of pharmacologic combination remedy with salmeterol and fluticasone on overall mortality in COPD was the TORCH trial (Toward a Revolution in COPD Health. The study originally involved 6,112 cases with moderate- to- severe COPD, and its primary endpoint was to compare the Effect of salmeterol/fluticasone versus placebo on all-cause Mortality over 3 years. The effect on all-cause mortality almost Reached statistical significance. Interestingly, careful analysis of the cause of individual deaths by a panel of experts showed That—in this population—the cause-specific mortality was 27% Cardiovascular, 35% respiratory, 21% cancer, 10% other, And 8% unknown. Forty percent of deaths were surely or presumably related to COPD. In addition, the effect of combination treatment, although statistically not significant, was nearly inversely distributed between respiratory and other causes, suggesting that this treatment also has nonpulmonary effects. The effects of inhaled steroids on mortality in patients with COPD is controversial. Corticosteroids that you take by mouth affect your entire body. For this reason, they are the most likely type of corticosteroid to cause side effects. Side effects depend on the dose of medication you receive and may include:

- A buildup of fluid, causing swelling in your lower legs.
- High blood pressure.
- Problems with mood swings, memory, behavior, and other psychological effects, such as confusion or delirium.
- Upset stomach.
- Weight gain in the belly, face and back of the neck

When taking corticosteroids by mouth for a longer term, you may experience:

- Problems with the eyes, such as glaucoma or cataracts.
- A round face, which is sometimes called moon face.
- High blood sugar, which can trigger or worsen diabetes.
- Increased risk of infections, especially with common bacterial, viral and fungal microorganisms.
- Bone fractures and thinning bones, called osteoporosis.
- Fatigue, loss of appetite, nausea and muscle weakness.
- Thin skin, bruising and slower wound healing.

Side effects of inhaled corticosteroids

When using a corticosteroid that you breathe in, some of the drug may deposit in your mouth and throat instead of making it to your lungs. This can cause:

- Fungal infection in the mouth, known as oral thrush.
- Hoarseness.

You may be able to avoid mouth and throat irritation if you gargle and rinse your mouth with water after each puff on your corticosteroid inhaler. Be sure not to swallow the rinse water. Some researchers think that inhaled corticosteroid drugs may slow growth rates in children who use them for asthma.(29–32)

Side effects of topical corticosteroids

Topical corticosteroids can lead to thin skin, skin lesions and acne.

Side effects of injected corticosteroids

Injected corticosteroids can cause temporary side effects near the site of the shot. These side effects include skin thinning, loss of color in the skin and intense pain. This pain is known as post-injection flare. Other symptoms may include facial flushing, insomnia, and high blood sugar. Health care providers usually limit corticosteroid injections to three or four a year, depending on each person's situation(33–37)

A pooled analysis, grounded on intention to treat, of individual patient data from seven randomized trials of At least 12 months' duration in patients with stable COPD Suggested that inhaled corticosteroids may markedly reduce all-Cause mortality (84). However, the 3-year prospective TORCH Study not only did not confirm the effect on mortality, but it Showed trend toward increased mortality in cases treated with inhaled corticosteroids alone. This striking distinction should further recommend that retrospective analysis be considered purely thesis generating, rather than solid evidence(2).

Conclusion:

This article discusses the significant impact, measurement, mechanisms, and management of comorbidities in Chronic Obstructive Pulmonary Disease (COPD). It highlights the growing global burden of COPD and its association with various comorbid conditions, particularly those related to cardiovascular and respiratory health. The article emphasizes that COPD is not just a lung disease but a complex, multi-component condition characterized by chronic systemic inflammation. Comorbidities are common in COPD, affecting patients at any stage of the disease. These comorbidities can include chronic heart failure, hypertension, skeletal muscle abnormalities, diabetes, osteoporosis, and more. Smoking, the primary risk factor for COPD, is also a major contributor to these comorbidities. Furthermore, the impact of comorbidities on the quality of life for COPD patients is significant. As the number of comorbidities increases, the self-reported health status and quality of life decrease. Comorbid conditions like heart failure, diabetes, and arthritis are associated with a decline in quality of life. The article discusses various measurement and assessment approaches for comorbidities in COPD, highlighting the limitations of relying solely on traditional lung function tests like FEV1. It introduces several multidimensional indices developed to assess COPD and its comorbidities, emphasizing the need for a more comprehensive approach to patient care. Mechanisms of COPD and its comorbidities, such as smoking, hypoxia, inflammation, endothelial dysfunction, platelet reactivity, arterial stiffness, and coronary artery disease, are explored. The interplay of these factors underscores the complex nature of the disease.

The management approaches for COPD patients with comorbidities include supplemental oxygen therapy and pharmacologic treatment. Long-term oxygen therapy has been shown to have beneficial effects beyond the lungs, improving various aspects of the patient's health. Pharmacologic treatments, particularly combination therapies, have been studied for their impact on mortality, with mixed results. Overall, the article highlights the need for a comprehensive and multidisciplinary approach to managing COPD and its associated comorbidities. It suggests that COPD is not merely a respiratory disease and should be addressed in a broader context to improve the overall health and quality of life of affected individuals. Additionally, ongoing research and clinical trials are essential to better understand the relationships between COPD and comorbid conditions and to develop effective treatments. Corticosteroid used in COPD leads to beneficial or harmful also which is cause of multiple chronic condition. So, monitor it's dosage regimen and get it's best alternative.

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