Prevention of Chronic Obstructive Pulmonary Disease (COPD) Exacerbations with Statin Therapy: A Systematic Review

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Abstract

This systematic review focuses on examining the treatment of chronic obstructive pulmonary disease (COPD) and preventing exacerbations. Despite the pharmacological interventions available, chronic obstructive pulmonary disease (COPD) is not curable. The goal of treatment in chronic obstructive pulmonary disease (COPD) patients is more focused on providing relief of symptoms such as dyspnea and shortness of breath. The purpose is to review the efficacy of daily Statin use in patients with newly diagnosed chronic obstructive pulmonary disease (COPD). This systematic review follows the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines 2020 and a search strategy was conducted using a variety of reputable databases such as PubMed, Google Scholar, Science Direct, and Research Gate. Of the 595 studies identified based on the selection of databases, 10 were selected for the final inclusion in the study. This review also highlights chronic obstructive pulmonary disease (COPD) pathophysiology, diagnosis, and treatment. The review provides a discussion section that demonstrated the outcomes of chronic obstructive pulmonary disease (COPD) exacerbations in patients on a daily regimen of Statins.

Categories: Anesthesiology, Internal Medicine, Pulmonology Keywords: intubation, inflammation, Statin therapy, acute exacerbation of chronic obstructive pulmonary disease, COPD: chronic obstructive pulmonary disease.

Introduction and Background

In 2019, the third leading cause of death worldwide was chronic obstructive pulmonary disease, causing 3.23 million deaths [1]. It was studied that smoking was the number one cause of COPD in over 70% of individuals who resided in high-income countries, with the USA being a major one [1]. According to the Centers for disease control Prevention, more than 50% of individuals with low pulmonary function test values were not conscious of the fact that they had an underlying lung pathology [2]. Another interesting fact is that in the past, COPD was thought to be present only in men [3]. However, studies have shown that women have had a higher mortality rate than men due to COPD since 2000 [3]. It could be due to delaying diagnosis or the initiation of disease in women starting at a younger age. In a patient who is severely ill from COPD, the challenge emerges when there is a decision to make whether to intubate the patient or if the patient would be better off with palliative care [4]. Chronic obstructive pulmonary disease is an umbrella term for other lung pathologies as well, including chronic bronchitis and emphysema [5]. These illnesses present differently clinically in a patient but lead to irreversible changes in the lungs. Chronic bronchitis is a process in which mucus is overproduced and secreted causing the epithelial cells in the lung to release inflammatory mediators in response. This leads to edema and reduced function and obstruction of the small airways which clinically leads to shortness of breath. [5,6]. On the contrary, emphysema initiates an insult to the alveoli which could be due to the radicals released from inhaled tobacco. The imbalance of proteases and antiproteases causes damage. The irritants from the tobacco reduce the function of the anti-protease proteins otherwise known as alpha antitrypsin that serves as a protection from oxidative stress. [6,7]. This causes an increase in the inflammatory proteolytic enzymes that destroy the alveoli. This destruction causes an irreversible inhibition of recoiling that limits gas exchange [7]. Therefore, carbon dioxide retention occurs and patients become hypoxic and hypercapnic. Chronically ill patients usually require mechanical ventilation when they go into acute hypoxic respiratory failure. The protocol in acute hypoxic respiratory failure is to first put the patient on a nasal cannula, if ineffective, the patient can proceed to a non-rebreather mask or high flow. If bilevel-positive airway pressure (BiPAP) does not meet oxygen demands, then the last resort is to intubate the patient. In a critically ill patient, the risks of intubation are far more than their benefits [8]. Mechanical ventilation or intubation is an invasive procedure and can lead to complications such as barotrauma, hyperinflation of the lungs, cardiac arrest, and even death. Therefore, ventilation is usually reserved as a last resort in patients with COPD who are critically ill [8]. Unplanned ventilation in the setting of respiratory failure can result in mortality [9]. A few of the complications related to intubation include aspiration and laryngeal trauma, especially in older patients [9]. Various medications
serve to aim at managing chronic obstructive pulmonary disease effectively. The first goal of treating COPD is to reduce oxidative stress by abstaining from smoking. Studies have shown that those individuals who quit smoking for 10 years have decreased his/her chances of lung cancer to about onehalf compared to the person who continues to smoke [10]. In the past decades, the management of COPD was geared toward the utilization of bronchodilators and corticosteroids. Studies have shown that stains play a role in preventing the progression of COPD. This could be due to their anti-inflammatory effects and could potentially reduce mortality in patients suffering from COPD [10]. This systematic review will aim to discuss the efficacy of Statins in avoiding mechanical ventilation in patients with COPD.

**Review**

**Methods**

**Search Strategy**

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines [11]. A search strategy was developed utilizing the following databases: PubMed, Science Direct, Google Scholar, and Research Gate. The search terms included “COPD”, “Statin”, “emphysema/etiology”, and “emphysema/pathophysiology.” A precise and pertinent list of articles was selected using the Boolean operator and medical subject headings (mesh) terms. The table below provides an overview of the databases selected for the review. A total of 310 articles were selected for potential review. After applying the inclusion and exclusion criteria, a total of 10 articles were selected for the final investigation of this systematic review. The summary of the search strategy and databases utilized for collection of articles is shown in Table 1.

<table>
<thead>
<tr>
<th>Search strategy</th>
<th>Database Utilized</th>
<th>Number of research articles identified</th>
<th>Date Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>“COPD” AND “intubation” AND “Statin”</td>
<td>Science Direct</td>
<td>101</td>
<td>2012-2023</td>
</tr>
<tr>
<td>“COPD” AND “intubation” AND “Statin”</td>
<td>Google Scholar</td>
<td>542</td>
<td>2012-2023</td>
</tr>
<tr>
<td>“COPD” AND “Statin”</td>
<td>Research Gate</td>
<td>60</td>
<td>2012-2023</td>
</tr>
</tbody>
</table>

Based on the following participants, intervention, and outcomes, the studies were selected for inclusion: Participants: Adults (>= 45 years) regardless of ethnicity and gender, with an established diagnosis of chronic obstructive pulmonary disease (COPD).

**Intervention**: Use of Statin therapy in the population mentioned above.

**Outcomes**: Statin therapy seems to be beneficial in preventing chronic obstructive pulmonary disease (COPD) exacerbations, reducing hospital visits, and providing symptomatic relief in individuals.

**Inclusion and Exclusion Criteria**

The following inclusion criteria were established for the systematic review: the main focus of the review were studies that were published in English, free-full texts published within the last 20 years, cohort studies, case studies, meta-analyses, and systematic reviews. On the contrary, the study excluded any publications not in English. It also excluded studies conducted on animals and those conducted on individuals without chronic obstructive pulmonary disease. Finally, gray literature and conference papers were not included in the study.

**Results**

Using the search strategies and reputable databases, a total of 595 articles were identified from the databases. These articles were published within the last 20 years. The articles were then removed if duplicates were recorded or for any reasons explained. The remaining articles were subjected to quality assessment by using quality assessment tools such as AMSTAR2 (for systematic reviews and meta-analyses), SANRA (for narrative review articles), the JBI quality appraisal checklist (for case series and case reports), and the Newcastle Ottawa checklist (for case-control and cohort studies). The PRISMA chart, an overview of the screening process, is shown in Figure 1.
FIGURE 1: PRISMA chart, an overview of the screening process

AMSTAR2: Assessment of Multiple Systematic Reviews 2
SANRA: Scale for the Quality Assessment of Narrative Review Articles
JBI Checklist Appraisal Checklist: Joanna Briggs Institute Critical Appraisal Checklist
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

The summary of the key findings are listed in Table 2.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Participants</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajmera et al [1].</td>
<td>Retrospective Cohort Study</td>
<td>19,060 Medicaid beneficiaries with newly diagnosed COPD</td>
<td>Statins have beneficial effects in patients with newly diagnosed COPD and reduced the number of copd-related hospitalizations and emergency visits requiring intubation.</td>
</tr>
<tr>
<td>Criner et al [2].</td>
<td>Prospective analysis</td>
<td>881 patients with diagnosed COPD</td>
<td>A daily dose of 40 mg Atorvastatin did not affect the exacerbation rates of a first time exacerbation for those patients with high-risk.</td>
</tr>
<tr>
<td>Freyburg et al [3].</td>
<td>Randomized control trials</td>
<td>107,301 patients with COPD.</td>
<td>Low LDL cholesterol was associated with increased risks of severe COPD exacerbation and COPD-specific mortality in the Danish general population. As this is opposite of that observed in randomized controlled trials with Statins, our findings might be a result of reverse causation indicating that individuals with severe phenotypes of COPD have lower plasma levels of LDL cholesterol due to wasting.</td>
</tr>
<tr>
<td>Mortensen et al [5].</td>
<td>Retrospective Cohort Study</td>
<td>11,212 with a mean age of 74 who were diagnosed with COPD exacerbation</td>
<td>Use of tattins and ACE inhibitors prior to admission is associated with decreased mortality in subjects hospitalized with a COPD exacerbation. Randomized controlled trials are needed to examine whether the use of these medications are protective for those patients with COPD exacerbations.</td>
</tr>
<tr>
<td>Soyseth et al [4].</td>
<td>Retrospective Cohort Study</td>
<td>854 patients with COPD exacerbation</td>
<td>Patients with COPD exacerbation benefitted from Statins which improved mortality but the use of glucocorticoids also increased survival benefit when utilized alongside with Statins.</td>
</tr>
<tr>
<td>Zhang W. et al [6].</td>
<td>Retrospective analysis</td>
<td>1,471 patients with COPD and coexisting cardiovascular disease</td>
<td>The findings demonstrated from this robust systematic review suggested that Statins play a role in patients with COPD and other co-existing comorbidities such as cardiovascular disease. The use of Statins reduced systemic inflammation and improved exercise tolerance and pulmonary function.</td>
</tr>
<tr>
<td>Manechotsuwansuk et al [7].</td>
<td>Randomized controlled trials</td>
<td>30 patients with stable COPD on Simvastatin 20 mg daily</td>
<td>Simvastatin was beneficial in patients with stable COPD. The effects of a daily simvastatin regimen reduced inflammation by reversing the IL-17A/IL-10 markers. There was also markedly reduced sputum macrophages in these patients.</td>
</tr>
</tbody>
</table>
Chronic obstructive pulmonary disease can present with many complications, including exacerbation of the illness itself. In this study, we investigated the efficacy of daily Statin use in preventing exacerbations leading to mechanical intubation. Chronic obstructive pulmonary disease was once seen to be an illness related to men, but recent studies have investigated the increasing prevalence of COPD in women as well [11]. As severe as it seems, not only are the repercussions of COPD partially reversible, but some individuals are asymptomatic until the disease progresses to a point where there is no other option but intubation [12]. Treatment of COPD is usually initiated with airway smooth muscle bronchodilators such as albuterol [13]. Severe exacerbations can be managed with albuterol and a long-acting muscarinic agonist, an example being ipratropium, with an addition of a glucocorticoid [13]. However, studies have shown that initiation of a daily Statin can prevent COPD exacerbations [13]. The most common Statin prescribed in this study was simvastatin 40 mg daily and per trial, its use greatly reduced the number of exacerbations that led to hospitalizations [14].

**Pathophysiology**

The lungs contain immune defenses to combat any invaders that seem dangerous to the cells. The alveoli in the lungs are lined by two types of cells: Type 1 and type 2 cells. Type 1 cells are responsible for gas exchange while type 2 cells secrete a substance called surfactant which is responsible for regulating surface tension in the alveoli [15]. Type 2 cells are also capable of regenerating alveolar epithelium and upregulating proteins necessary for host defense [16]. Along with the type 1 and type 2 cells that are responsible for maintaining the alveolar function, some enzymes exist that have smoking can have devastating and fatal effects. Anti-proteases are the proteins that help against the oxidative stress from cigarette tobacco [16]. An imbalance of the protease and antiproteases lead to the destruction of lung tissue [17].

Figure 2 demonstrates the pathophysiology of emphysema, a component of chronic obstructive pulmonary disease [17].

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**TABLE 2:** Summary of the key findings from the studies COPD - chronic obstructive pulmonary disease IL - interleukin LDL - low-density lipoprotein

The findings from these studies above demonstrated that the addition of a Statin medication to the daily regimen of a patient with COPD showed a positive impact. Furthermore, the use of Statin showed a greater benefit in those individuals who suffered from COPD with a co-existing illness such as coronary artery disease or congestive heart failure. In one of the studies, simvastatin use also increased serum erythropoietin levels and markedly reduced serum uric acid levels [10]. The use of Statins and ace inhibitors provides substantial relief of symptoms in patients with COPD [5]. Statin use decreased the probability of exacerbations in participants with COPD (Odds ratio = 0.79, CI (confidence interval) = 0.74-0.85, p < 0.003). Overall, these findings highlight the importance of adding an anti-inflammatory medication that can improve the quality of life in these patients with COPD.
FIGURE 2: Pathophysiology of emphysema, a component of COPD COPD - chronic obstructive pulmonary disease MMP - matric metalloproteinases

The process of chronic obstructive pulmonary disease involves inflammation. The process of inflammation starts with macrophages, as they are defenders of the host immune system [16]. The main role of macrophages in the process of COPD is to release cytokines, chemokines, reactive oxygen species, and elastocytic proteins, which leads to the inflammatory process of COPD. Although their role is to recruit blood monocytes to fight oxidative stress, its effects are detrimental to the lungs [16].

Figure 3 demonstrates the inflammatory process in chronic obstructive pulmonary disease [16].

TGFβ: transforming growth factor beta
TH1: T-helper cells
TC1: type 1 cytotoxic T cells

Diagnosis The diagnosis of chronic obstructive pulmonary disease can be done clinically provided that the patient has experienced dyspnea, has had a productive cough, and has had a history of smoking, however, spirometry confirms the diagnosis [18]. Chronic obstructive pulmonary disease progresses very slowly and the individual is in a long asymptomatic phase where the lung function declines. In other words, COPD presents like a silent killer. Symptoms of chest pain, wheezing, and dyspnea with exercise do not clinically present until the forced expiratory volume under one second (FEV1) declines to 50% of the normal value [19]. Patients whose FEV1 is less than 80% of the normal value and whose ratio of FEV1 to forced vital capacity or the maximum expired volume is less than 70%, which relates to a high index of suspicion of COPD. This FEV1/FVC ratio of less than 70% is predictive of COPD after a trial of bronchodilator shows no response [20].

Table 3 presents spirometry measurements that can be used to classify the severity of chronic obstructive pulmonary disease [21].

<table>
<thead>
<tr>
<th>Stage</th>
<th>Level</th>
<th>Findings (post bronchodilator FEV1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>At risk</td>
<td>Risk factors present, chronic symptoms, but spirometry measurements normal</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
<td>FEV1/FVC &lt; 70% FEV1 80% of predicted value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic some</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>FEV1/FVC &lt; 70% FEV1 50% to &lt; 80% of predicted value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic chronic</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>FEV1/FVC &lt; 70% FEV1 30% to &lt; 50% of predicted value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic chronic</td>
</tr>
<tr>
<td>4</td>
<td>Very severe</td>
<td>FEV1/FVC &lt; 70% FEV1 &lt; 30% of predicted value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR FEV1 &lt; 50% of predicted value plus chronic symptoms</td>
</tr>
</tbody>
</table>

TABLE 3: Stages of chronic obstructive pulmonary disease (COPD) FEV1 - forced expiratory volume in one second FVC - forced vital capacity.

Although asthma is considered a part of chronic obstructive pulmonary disease, its distinction from emphysema and bronchitis is by its response to bronchodilators. A reversible response to bronchodilators is indicative of asthma [21]. COPD exacerbations account for 50% of total COPD costs in hospitals [22]. The exacerbations do not only come with financial costs, but the time to recovery is not easy and short. A COPD exacerbation is defined as an increase in symptoms from a normal day-to-day basis. This includes increased shortness of breath, cough, and sputum production [23]. Usually, a bacterial infection superimposes the disease process and causes the severity of symptoms [24]. The main microorganisms causing COPD exacerbations are Haemophilus influenza, Streptococcus pneumoniae, Moraxella catarrhalis, Pseudomonas aeruginosa, and Rhinovirus [25]. According to a study, patients with exacerbations did not return to baseline symptoms until 7 days following the acute exacerbation event [26]. In fact, in 14% of these events, most patients did not return to their baseline until 35 days after the onset of the event, and some patients never returned to their baseline and only progressed in their disease course [27]. Treatment The single most important factor in reducing mortality in the course of chronic obstructive pulmonary disease is the cessation of smoking [28]. Studies have shown that a 3-minute counseling session with patients led to 5-10% quitting rates [29]. Some medications are effective in the prevention of cravings such as nicotine gum and patches, the antidepressant Bupropion, and the nicotinic agonist Varenicline, alongside counseling [30]. No treatment has been shown to cure the disease itself, but the medications are rather for relieving symptoms [31]. Studies have stipulated that early detection has a role in preventing exacerbations and frequent emergency visits [31].
Figure 4 illustrates the pharmacological treatment of COPD depending on severity [32].

**FIGURE 4: Pharmacological treatment of COPD depending on severity mMRC - modified medical research council (dyspnea scale) CAT: COPD assessment test**

COPD exacerbations are mostly managed with a combination of short-acting inhaled β2 agonists (SABA) such as albuterol and long-acting muscarinic antagonists (LAMA) like ipratropium [32].

Glucocorticoids are also effective when given as an adjunct with albuterol and ipratropium in reducing inflammation [33]. Studies have shown that the use of daily Statins improved clinical outcomes in patients with COPD [33]. The use of daily Statins reduced the number of hospital visits and increased the time from diagnosis of COPD to an acute episode of exacerbation [34]. In the Copenhagen General Population Study, it was demonstrated that Statins reduced the risk of exacerbations in patients with COPD long with a comorbid condition of coronary artery disease [34]. Statins play a role in reducing inflammation by inducing the cellular accumulation of endothelial nitric oxide synthase which thus hinders the expression of adhesion molecules that recruit inflammatory cells. Statins are effective in inhibiting the proliferation of vascular smooth muscle cells and inducing apoptosis [35]. The anti-inflammatory properties of Statins have clinically demonstrated a reduced risk of COPD exacerbations [35].

**Strengths**

This systematic review presents many strengths. The study follows the PRISMA guidelines, which ensures an efficient approach to searching for article collections, quality assessment of the chosen articles, and proper data extraction. The review also included a comprehensive search strategy that extracted the proper data from credible databases. The review also provided data from all ethnicities, reducing any selection bias for data collection. Finally, the systematic review provides a discussion section that thoroughly explains the pathophysiology of chronic obstructive pulmonary disease, explores explanations for the study findings, and proposes future research directions.

**Limitations**

Even though this study has its strengths, there are some weaknesses. First, the systematic review mainly focuses on retrospective cohort studies. Second, the systematic review focuses on studies conducted worldwide, so it considers many factors that may lead to COPD, rather than just smoking. For example, in India, many individuals suffer from bronchitis not due to smoking but because of recurrent tuberculosis. The review focuses on patients with not only COPD but other comorbid conditions such as coronary artery disease, which may affect the outcomes of the proposed research. Future studies might need to consider the mean age when Statins should be initiated, perhaps when COPD is newly diagnosed. Compliance with medications is also a limitation that we are unaware of in these studies.

**Conclusions**

This systematic review focused on the treatment of chronic obstructive pulmonary disease and the effects of Statins to prevent exacerbations. Findings from selected articles demonstrated significant benefits of adding a daily regimen of Statins in a patient with newly diagnosed chronic obstructive pulmonary disease. The analysis highlighted the pathophysiology, diagnosis, and treatment of COPD and exacerbations. Despite the current treatment available, Statins did lead to a positive outcome in those with COPD. Further research should be conducted in newly diagnosed COPD patients without any comorbid conditions to provide a clear understanding of the efficacy of Statins.

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Keywords: COPD, statins, inflammation, chronic obstructive pulmonary disease exacerbations, emphysema, albuterol

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