Persistent systemic inflammation and symptoms of depression among patients with COPD in the ECLIPSE cohort

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KEYWORDS
Chronic Obstructive Pulmonary Disease; Depressive disorder; Psychological symptoms; Comorbidities;

Summary
Background: Depression is highly prevalent among patients with Chronic Obstructive Pulmonary Disease (COPD). The relationship of depression with systemic inflammation in COPD remains unknown. The objective of this observational study was to compare depression scores at baseline and after 36 months follow-up between COPD patients with persistent systemic inflammation (PSI) and never inflamed patients (NI) in the ECLIPSE cohort.
Methods: The ECLIPSE study included 2164 COPD patients. Parameters assessed at baseline and at 36 months follow-up included: demographics, clinical characteristics and symptoms

Abbreviations: PSI, persistent systemic inflammation; NI, never inflamed patients.
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Introduction

Although Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent and often progressive airflow limitation, comorbidities contribute to the severity of the disease [1]. Depression is a frequent COPD comorbidity which is often underdiagnosed and undertreated [2], but clinically relevant. For instance, depression scores are worse among COPD patients with frequent exacerbations [3], and mortality is higher in patients hospitalized because of an acute exacerbation and clinically relevant symptoms of depression [4]. A recent systematic review showed a bidirectional relationship between COPD and depression where COPD increases the risk of developing depression, and depression is associated with worse outcomes in COPD [5].

The pathobiology of depression in COPD is unclear. Previous cross-sectional analysis of the ECLIPSE ('Evaluation of COPD Longitudinally to Identify Predictive Surrogates End-points') study identified several clinical determinants of depression (assessed by the Center for Epidemiologic Studies of Depression, CES-D). Patients classified as NI had zero and patients with PSI had ≥2 inflammatory biomarkers (white blood cell count, hsCRP, IL-6, and fibrinogen) in the upper quartile, at baseline and 12 months later.

Findings: 350 patients (29.1%) were NI and 131 patients (10.9%) had PSI. At baseline, mean CES-D score was higher in patients with PSI than in NI patients (11.7 (8.6) vs. 9.2 (8.9) points, \( p = 0.01 \)). Differences were not confirmed after adjustment for possible confounders (β (95% CI) = 0.02 (−3.87 to 15.29), adjusted \( p = 0.98 \)). At 36 months follow-up, CES-D scores were comparable in PSI and NI patients (12.2 (9.3) vs. 10.5 (9.0) points, \( p = 0.08 \)) as were their temporal changes (0.5 (8.3) vs. 1.3 (7.9) points, \( p = 0.30 \)).

Conclusion: The ECLIPSE study does not support a strong relationship between PSI and symptoms of depression at baseline and after 36 months follow-up in COPD.

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Material and methods

Study design

The present study is a secondary analysis of the ECLIPSE study (Clinicaltrials.gov identifier NCT00292552; GSK study code SCO104960), a multicenter, longitudinal, controlled, observational study, conducted in 12 countries whose methodology has been published in detail elsewhere [13]. Participants were assessed at baseline, three and six months, and then every six months for 36 months.

Study population and ethics

The ECLIPSE study recruited 2164 patients with COPD [14]. Patients were between 40 and 75 years of age, with a baseline post-bronchodilator forced expiratory volume in the first second (FEV₁) below 80% of the predicted value, and a FEV₁/forced vital capacity (FVC) ratio below or equal to 0.7 and a smoking history of 10 or more pack years. Patients were clinically stable, defined by the absence of any COPD exacerbation within four weeks preceding enrollment [13]. The current analysis is limited to patients with complete data on the primary outcome variables and possible confounders of the relationship between...
depression and systemic inflammation (350 NI patients and 131 patients with PSI).

The ECLIPSE study complies with the Declaration of Helsinki and Good Clinical Practice guidelines. Approval from the Medical Ethics Committees or Institutional Review Boards was obtained from all participating centers. All patients gave written informed consent [13].

Measurements

Demographic characteristics (age, sex, race, educational level) and clinical characteristics (body mass index (BMI), smoking status, number of pack years, long-term oxygen use, BODE index [15], history of depression, and antidepressant use) were recorded at baseline and during follow-up visits. Spirometry and the six-minute walk tests were performed according to international guidelines [16,17]. The number of exacerbations during 36 months follow-up was recorded using monthly phone calls and scheduled study visits [13].

Symptoms of depression during the previous week were measured at baseline and after 36 months follow-up using the CES-D, a self-administered questionnaire consisting of 20 items [18]. Each item is scored on a four-point scale ranging from 'rarely or none of the time' to 'most or all of the time'. Total score ranges from 0 (best) to 60 (worst) points. A score of 16 points and higher indicates clinically relevant symptoms of depression (sensitivity 0.73; specificity 0.84) [18]. Test–retest reliability is estimated at 0.71 [19].

Severity of dyspnea was measured using the modified Medical Research Council dyspnea scale (mMRC) at baseline and every year [20]. Disease-specific health status was measured using the St. George Respiratory Questionnaire for COPD patients (SGRQ-C) at baseline and every year. Total scores range from 0 (no impairment) to 100 (worst possible health status) points [21].

Peripheral venous blood was collected in the morning, after fasting overnight, at baseline and at one year follow-up to measure biomarkers. Details of biomarkers measurement have been published before [12]. PSI was defined as the presence, both at baseline and after one year follow-up, of two or more of the following biomarkers in the upper quartile: white blood cell (WBC) count, hsCRP, IL-6, and fibrinogen [12]. Patients were classified as NI when none of these biomarkers was in the upper quartile at baseline or after one year follow-up [12].

Statistical analysis

Results are presented as mean (SD), median (SD), and/or proportions, as appropriate. Demographics, clinical characteristics and CES-D scores were compared between NI patients and patients with PSI. Chi square tests were used for categorical variables. Independent sample T tests were used for normally distributed continuous variables, while Mann–Whitney U tests were used for continuous variables that were not normally distributed. Changes between baseline and 36 months in CES-D scores were compared using paired T-tests, after stratification for presence of PSI. Linear regression models were used to examine the association between PSI and CES-D score at baseline and 36 months, where CES-D score was the dependent variable, PSI the independent one and a number of patient characteristics previously shown in the literature to have a relationship with symptoms of depression in patients with COPD were considered covariates. The latter include: age [4,6,22,23], sex [6,24], FEV1 (% pred.) [6], BMI [2,4,24], mMRC score [2,24], SGRQ total score [22], six-minute walking distance [25], smoking status [6], educational level [23] and number of exacerbations [3] (only in the model with CES-D score at 36 months as dependent variable). Analyses were done using SPSS v.19.0. A two-sided level of significance was set at \( p \leq 0.05 \).

Role of the funding source

GlaxoSmithKline had a role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

Patient population

ECLIPSE recruited 2164 patients with COPD. Of these, 211 died during 36 months follow-up (9.8%), 286 (13.2%) withdrew because of other reasons, and 466 (21.5%) had incomplete data on the primary outcome variables or possible confounders of the relationship between PSI and depression either at baseline or 36 months later. Hence, 131 patients (10.9%) with PSI and 350 NI patients (29.1%) were finally included in the current analysis (total 481 patients, 22.2% of the original cohort).

Patient characteristics stratified by systemic inflammation

Table 1 shows that, compared to NI patients, those with PSI had higher BMI, lower FEV1, were more often current smokers, were more likely to have been prescribed long-term oxygen therapy, had worse exercise capacity, more dyspnea, worse disease-specific health status and higher BODE index. They also experienced more exacerbations during follow-up than NI patients (median (IQR): 3.0 (1.0–5.0) vs. 2.0 (0.0–4.0), \( p < 0.001 \)).

Symptoms of depression at baseline in NI and PSI patients

At baseline, mean CES-D score was higher in patients with PSI than in NI patients (\( p = 0.01 \)) (Table 2). However, after adjustment for possible confounders in linear regression analysis, CES-D scores were comparable between patients with and without PSI (\( \beta \) (95% CI) = 0.02 (–3.87 to 15.29), adjusted \( p = 0.98 \)) (Table 3). By contrast, mMRC score and SGRQ total score emerged as significant determinants of depression in COPD. Higher mMRC score was related with lower CES-D score, while higher SGRQ total score was related with higher CES-D score. When the same analysis
was performed in the sample with complete baseline data (n = 585), irrespective of the fact that some patients died or withdrew from the study during follow-up, baseline CES-D scores were also comparable between NI and PSI patients (b (95% CI) = 0.63 (−0.95 to 2.20), adjusted p = 0.44). Finally, history of depression and antidepressant use at baseline was similar in NI patients and patients with PSI (p = 0.84 and p = 0.44, respectively) (Table 2).

Changes in symptoms of depression during 36 months follow-up

Mean CES-D scores remained unchanged after 36 months in PSI patients (p = 0.50). Mean CES-D scores increased slightly but significantly in NI patients (p = 0.002). At 36 months a trend was suggested towards higher CES-D scores in patients with PSI compared to NI patients (p = 0.08) (Fig. 1). This was not confirmed by linear regression analysis after correction for the aforementioned possible confounders (b (95% CI) = −0.66 (−2.38 to 1.06), adjusted p = 0.45). In addition, there were no statistically significant differences in mean changes in CES-D scores between baseline and 36 months between patients with PSI and NI patients (p = 0.30). Finally, the proportion of patients who developed clinically relevant symptoms of depression or recovered from clinically relevant symptoms of depression was comparable between patients with PSI and NI patients (p = 0.66 and p = 0.15, respectively, Table 2).

Discussion

The key findings of this observational study in 481 patients with COPD are that: (1) the presence of PSI is not related to clinically relevant symptoms of depression at baseline,
after 36 months follow-up or to their change over time, after correction for potential confounders; and, (2) the main determinants of symptoms of depression in this population were dyspnea and disease-specific health status. Overall, these results do not support our working hypothesis but contribute to better understand the determinants of depression in COPD, a frequent and clinically relevant comorbidity in these patients.

The present study found that mean CES-D scores increased significantly (+1.3 points) in NI patients after 36 months, while mean CES-D scores remained unchanged after 36 months in PSI patients. To date, a minimal clinical important difference for the CES-D remains unknown, which makes it difficult to interpret these findings. However, a French population study showed mean CES-D changes between +0.4 and +2.5 points over three years [26], while another study among healthy individuals found a decrease of 1.2 points after one year [27]. Moreover, previous authors studying an intervention in primary care patients with a newly diagnosed depression defined a change of 3.6 points over 6 months as a relevant change [28]. Therefore, the clinical relevance of the statistically significant change in CES-D score over three years among NI patients seems limited.

Previous studies

A number of previous studies have investigated potential general mechanisms linking systemic inflammation and depression, including a direct effect on neuronal function [29], the activation of the hypothalamus–pituitary–adrenal axis [29] and/or oxidative stress [30]. Besides, a study in the general population suggested that there may be a relationship between systemic inflammation and depression subtypes, because the subgroup of younger adults with atypical major depressive disorder had higher CRP levels [31].

In the context of COPD, three previous studies are worth noting. Firstly, Al-shair et al. found a positive correlation between TNF-α (but not other inflammatory markers like CRP, TNF-α-R1, TNF-α-R2, and IL-6) and the BASDEC depression score in stable patients with moderate COPD, after adjusting for potential confounders [7]. In our study we did not include TNF-α in the definition of PSI because it may be a marker of smoking rather than COPD [12]. However, a previous ECLIPSE publication did not find any relationship between CES-D scores and TNF-α [6]. Secondly, Eagan et al. showed a relationship between TNFR-1 and depression requiring treatment in patients with COPD, after correction for possible confounders [8]. We did not include TNFR-1 in the definition of PSI and, in fact, a previous ECLIPSE analysis showed no difference in TNFR-1 between persons with or without COPD [32]. Thirdly, in line with our findings, Thomsen et al. showed no relationship between the combination of CRP, fibrinogen, and leukocyte count at baseline and hospital admission because of depression within five year follow-up after adjustment for potential confounders among 8571 subjects with COPD identified from a Danish general population sample [33].

Interpretation of findings

Although poorly understood, mechanisms underlying depression in COPD are likely multifactorial and may include biological, disease-related and social factors [34]. The former include, among others, genetic factors that may drive nicotine addiction and COPD development [34] and

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**Table 3** Relationship between baseline CES-D score and presence of PSI: linear regression analysis.

<table>
<thead>
<tr>
<th>Primary predictor</th>
<th>Beta (95% CI)</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSI (ref: no)</td>
<td>0.02 (-3.87 to 15.29)</td>
<td>0.98</td>
</tr>
<tr>
<td>Covariates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.09 (-0.20 to 0.02)</td>
<td>0.11</td>
</tr>
<tr>
<td>Sex (ref: female)</td>
<td>-1.25 (-2.82 to 0.33)</td>
<td>0.12</td>
</tr>
<tr>
<td>Educational level (ref: less than high school)</td>
<td>-1.38 (-3.05 to 0.29)</td>
<td>0.11</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.01 (-0.15 to 0.14)</td>
<td>0.91</td>
</tr>
<tr>
<td>Post bronchodilator FEV1 (% pred.)</td>
<td>0.04 (-0.02 to 0.09)</td>
<td>0.18</td>
</tr>
<tr>
<td>Current smoker (ref: non-smoker)</td>
<td>0.22 (-1.37 to 1.80)</td>
<td>0.79</td>
</tr>
<tr>
<td>6 min walking distance</td>
<td>-0.00 (-0.01 to 0.01)</td>
<td>0.67</td>
</tr>
<tr>
<td>mMRC score</td>
<td>-1.27 (-2.24 to -0.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>SGRQ-C total score</td>
<td>0.25 (0.20 to 0.30)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

n = 481. r² = 0.24, p < 0.001. Abbreviations: see legend Table 1. CI = Confidence Interval.
poor brain oxygenation, particularly in the periventricular and subcortical regions [35]. COPD itself can equally lead to symptoms of depression [35] through, for instance, limitations in daily activities [34]. Finally, social factors may also be important since poor family support appears to be associated with depression in COPD [36]. The relationship between depression and disease-specific health status in COPD is well-known [2,22]. We were unable to find a relationship between PSI and depression, although we found a univariate relationship between PSI and disease-specific health status. Our study confirms the important relationship between symptoms of depression and the impact of COPD. Indeed, symptoms and disease-specific health status are more important determinants of depression than biological factors such as FEV₁ or PSI. Comparable results were found among patients with rheumatoid arthritis. A study by Low et al. [37] suggested a relationship between symptoms of depression and CRP in women with rheumatoid arthritis. However, after adjustment for pain and disability this relationship was no longer significant. This emphasizes the importance of interventions aimed to reduce the impact of chronic diseases. For instance, pulmonary rehabilitation has been shown to improve symptom burden, disease-specific health status, exercise tolerance, the ability to cope with COPD as well as symptoms of depression [38].

Potential limitations

Our study has several potential limitations that deserve comment. Firstly, we only included patients who completed at least one year follow-up. Therefore, it is unknown if our observations can be applied to patients with less than one year survival. Secondly, symptoms of depression were assessed using the CES-D that measures the presence of clinically relevant symptoms of depression in the previous week. This may limit the identification of a relationship between symptoms of depression and PSI, albeit it is of note that we did not find either a relationship between PSI and history of depression or use of antidepressants. Third, inflammatory biomarkers were only measured at baseline and after one year. Therefore, stability of PSI in this cohort is unknown. Finally, our study classified subjects as persistently inflamed vs. non-inflamed using an index we previously have related to other relevant symptoms of depression [35]. COPD itself can equally lead to poor brain oxygenation, particularly in the periventricular and subcortical regions [35].

Conclusions and implications for future studies

Our study is the first to explore the relationship between symptoms of depression in COPD patients and PSI, both at baseline and after one year follow-up. Our findings do not support a strong relationship with PSI but, given that depression is not a homogenous entity [34], before completely rejecting our hypothesis, it might be reasonable to explore the relationship between PSI and several subtypes of major depressive disorders in COPD. On the other hand, our longitudinal results confirm previous cross-sectional analysis that identified symptoms and impaired health status as major determinants of symptoms of depression. This emphasizes the importance of therapeutic interventions aimed to reduce the impact of COPD, such as pulmonary rehabilitation [38].

Author contributions

Design and performance of the ECLIPSE study: AA, HM, JCY, RTS, SIR, JV, EFMW. Design of the current analyses: DJAJ; AA, HM, EFMW. Data-analysis: DJAJ. Interpretation of the results: DJAJ, AA, HM, JCY, RTS, SIR, JV, EFMW. Drafting of the manuscript: DJAJ. Revising and final approval of the manuscript: DJAJ, AA, HM, JCY, RTS, SIR, JV, EFMW. DJAJ had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interest

DJAJ has received lecture fees from GlaxoSmithKline and Astra Zeneca.

AA is a member of the Scientific Committee of ECLIPSE. He has received honorarium for speaking, participating in advisory boards and/or research funds from Almirall, Astra Zeneca, Boheringer-Ingelheim, Chiesi, GSK, Kyorin, Menarini, MSD, Novartis, Takeda and Wiley.

HM is employee and shareholder of GlaxoSmithKline.

JCY is employee and shareholder of GlaxoSmithKline.

RTS is employee and shareholder of GlaxoSmithKline.

SIR has had or currently has a number of relationships with the following companies: Align2Action, HealthStar, Almirall, Janssen Research and Development, Boehringer Ingelheim, LEK, Decision Resources, McKinsey, Dunn Group, Merck, Easton Associates, Navigant, Elevation Pharma, Penn Technology, Forest, Strategic North, Gerson, Synapse Gilead, Telecon SC, GlaxoSmithKline, CME Incite, Nuvis, Pro-iMed, Incite, Takeda IntraMed (Forest), Astra Zeneca, Pearl, Pfizer, Johnson & Johnson, APT, Merck, Nycomed and Prescott. These relationships include serving as a consultant, advising regarding clinical trials, speaking at continuing medical education programs and performing funded research both at basic and clinical levels.

JV received fees for advising and/or presenting from GlaxoSmithKline, Astra Zeneca, Pfizer, Boehringer-Ingelheim, Nycomed, Hofmann — la Roche, Talecris, Kamada and Sounds Biotech; has received research support from GlaxoSmithKline.

EFMW serves on an advisory board for Nycomed. EFMW has received lecture fees from GlaxoSmithKline, Astra Zeneca and Novartis, and has received research grants from GlaxoSmithKline and Astra Zeneca.

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