The risk of depression in chronic obstructive pulmonary disease

Tadeusz Pietras[1], Andrzej Witusik[2], Michał Panek[3], Paweł Górski[1], Piotr Kuna[3]

[1]Department of Pneumology and Allergology, Medical University of Lodz, Poland
Head: Prof. Paweł Górski MD, PhD
[2]Department of Psychology, Jan Kochanowski University of Humanities and Sciences, Piotrkow Trybunalski, Poland
Head: Andrzej Witusik PhD
[3]Department of Internal Diseases, Asthma and Allergy, Medical University of Lodz, Poland
Head: Prof. Piotr Kuna MD, PhD

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Abstract

Introduction: Chronic obstructive pulmonary disease is a severe systemic disease compromising to a large extent the quality of life due to dyspnea, recurrent infections, life-threatening conditions, considerable impairment of the patient's social activity. Additionally, systemic inflammation accompanying the disease may affect central neurotransmission, thus contributing to the development of depression.

Aim: The aim of the research was to assess the risk of mood disturbances in COPD patients as well as to estimate the risk level according to severity of the disease.

Material and methods: The study was carried out on 174 patients with COPD and 121 healthy patients. All of them underwent spirometry to assess the flow-volume curve and to determine the severity of COPD according to the GOLD standard, as well as psychiatric examinations to diagnose depression episodes. Each patient was also assessed with the Beck Depression Inventory.

Results: The relative risk of mood disturbances in COPD patients as compared with subjects without COPD was estimated to amount to 2.7007 (95% CI 1.3167-5.5393). Additionally, the increase of risk of mood disturbances in patients with first grade disease severity vs. healthy controls and patients with second grade disease severity vs. controls did not reach statistical significance – the obtained results were: 0.8219 (95% CI 0.2911-2.3202) and 1.5909 (0.5794-4.3683), respectively. For third grade COPD severity patients vs. healthy controls, the relative risk was estimated at 5.000 (95% CI 1.8766-13.3223) and was statistically significant, similarly to fourth grade severity patients vs. the control group (OR 20, 95% CI 6.6654-60.0112). The mean level of depression in the group of COPD patients was 8.51 ±4.18, in the group without COPD – 7.19 ±3.67; the difference was significant statistically (p = 0.005637). For patients with first grade disease severity, the mean score obtained according to the Beck Depression Inventory was 7.27 ±2.83, for second grade severity – 7.58 ±4.35, for third grade – 10.26 ±3.99, and for the fourth grade – 12.57 ±5.20. The coefficient of correlation between the results of the Beck Depression Inventory and FEV1 percentage values as compared with normal FEV1 obtained for the overall population of COPD patients was negative: r = –0.466011, p = 0.000.

Conclusions: Development of chronic obstructive pulmonary disease increases the relative risk of a depression episode. This risk increases with the increase of disease severity assessed according to the GOLD grading standard.

Key words: chronic obstructive pulmonary disease, depression.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease affecting ca. Ten percent of the Polish population [1]. This disease is usually a consequence of nicotine addiction or, in rare cases, α1-antitrypsin deficiency [2, 3]. It is characterized by irreversible or poorly reversible bronchospasm, development of emphysematous bullae, chronic inflammatory condition of the respiratory tract. Chronic obstructive pulmonary disease leads to right ventricular cardiac insufficiency and respiratory failure [4]. As a severe somatic disease, COPD considerably compromises the quality of life [5, 6]. Poor quality of life results

Address for correspondence: Tadeusz Pietras MD, PhD, Department of Pneumology and Allergology, Medical University, 22 Kopcinskiego, 90-153 Lodz, Poland, phone: +48 42 678 75 05, +48 42 677 66 99, fax: +48 42 678 21 29, e-mail: cital200@wp.pl

in anxiety disorders and secondary depressive moods, therefore COPD is regarded as a risk factor for development of mood disturbances and anxiety disorder [5-7]. A question arises as to how high the risk of mood disturbances occurring in the course of COPD is [5, 6]. The association of mood disturbances with somatic diseases may result not only from the psychosomatic aspect of the disease. Mediators of inflammation, such as interleukin 1 (IL-1), IL-6, IL-8, tumor necrosis factor α (TNF-α), interferon, released in the course of chronic inflammatory conditions, affect neurotransmission so that they favor the development of mood disturbances [8, 9]. Systemic release of inflammatory mediators takes place also in COPD [4]. Such a phenomenon is frequently observed after the administration of interferon for therapeutic purposes [10-12].

Aim

The aim of the reported research was to assess the risk of mood disturbances in COPD patients as well as to estimate the risk level according to severity of the disease.

Material and methods

The study group consisted of 174 COPD patients (143 men and 31 women). All of the patients underwent routine examinations to assess the flow-volume curve with the aim to determine COPD severity grade according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) standard. The diagnosis of COPD was established according to the GOLD criteria, independently by two physicians. Patients with systemic collagenoses, renal insufficiency, history of stroke, dementia, Parkinson disease, hyperthyroidism, malignancies treated at the time of the study, were excluded. Subjects who had previously suffered from mood disturbances, including bipolar affective disorder, were not excluded from the study. In the studied population, first grade COPD according to the GOLD standard was diagnosed in 79 patients, second grade COPD in 44, third grade in 30 and fourth grade in 21 patients. Additionally, all the patients underwent a psychiatric examination for assessment of their actual mental state. Depression episodes were diagnosed using the ICD-10 criteria in the version adjusted to the Polish language [13]. Depression episodes were diagnosed by a psychiatrist who did not know the pneumological diagnosis. The diagnosed depression episodes were classified as mild (ICD-10 F32.0), moderate (F32.1) and severe (F32.2). None of the patients were diagnosed with severe depression episodes with psychotic symptoms. The course of mood disturbances was not analyzed because of short observation time. Among the studied COPD patients, one male smoker had confirmed bipolar affective disorder and demonstrated a mild depression episode of moderate intensity (ICD-10 F31.3) at the time of the study. All of the patients were additionally assessed using the Beck Depression Inventory in the version recommended by Wciórka and Pużyński [14]. The results were presented as the obtained scores.

The control group consisted of 121 subjects (99 men and 22 women) age-matched to the study group, remaining under care of the Department of Pneumology within the framework of prevention programs or followed up after respiratory tract infections. The control subjects underwent the same clinical assessment procedures as the COPD patients from the study group. The gender proportions were similar in both groups: the COPD group included 18.2% of women and the control group – 17.8% and the difference did not reach statistical significance ($\chi^2 = 0.109352$, $df = 1$, $p < 0.916716$). The gender variable was not subjected to further analysis because of too low number of women and similar proportions of women in both groups.

The average age in the study group was 62.3 ±2.3, in the control group – 60.01 ±2.7 and did not demonstrate a statistically significant difference between both groups. However, the groups differed in the history of nicotinism. There were 154 smokers among COPD patients, which accounted for 88.21%, whereas in the control group there were 57 active smokers, or ex-smokers – 47.10%. The difference was found to be statistically significant ($\chi^2 = 162.2037$, $p < 0.00$).

The participation in the study was voluntary. The patients were informed about the study objectives and declared their consent in writing. The study was approved by the Institutional Ethics Committee (Lodz Medical University Ethics Committee approval No. RNN/14/07/KE, issued on 16 January 2007).

Statistical calculations were performed using an IBM PC computer with the application of Statistica 5.1 PL (SN: SP818052912G5) statistical analysis software package. Statistical significance level was set at $p < 0.05$.

Results

The onset of COPD proved to be a risk factor for developing mood disturbances. In the group of COPD patients, 37 subjects met the criteria for a depression episode, vs. 11 among healthy controls. Out of 11 healthy subjects diagnosed with depression episodes, a moderate depression episode was observed in one case only, whereas in the remaining subjects it was mild. Among patients with first grade COPD, mild depression episodes were diagnosed in 6 cases, with second grade disease severity – in 7 cases (including one person with a moderate depression episode), with third grade COPD – mild depression episodes were observed in 10 subjects, with third/fourth grade COPD – in 14, including 2 subjects with moderate depression episodes.

The relative risk of depression in different COPD severity grades compared with one another and with healthy subjects has been presented in Table 1. As it follows from

Table 1. Relative depression episode risk

Risk of depression in group A vs. group B	OR value	95% CI	Statistical significance
Risk of occurrence of any depression episode in the group of COPD patients vs. healthy controls	2.7007	1.3167-5.5393	Statistically significant
Risk of occurrence of a moderate or severe depression episode in the group of COPD patients vs. healthy controls	2.709	0.2781-26.3931	Statistically insignificant
Risk of occurrence of a depression episode in the group of second grade COPD patients vs. first grade COPD group	2.3018	0.7216-7.3423	Statistically insignificant
Risk of occurrence of a depression episode in the group of third grade COPD patients vs. first grade COPD group	6.0833	1.9719-18.7671	Statistically significant
Risk of occurrence of a depression episode in the group of fourth grade COPD patients vs. first grade COPD group	24.333	7.1032-83.3578	Statistically significant
Risk of occurrence of a depression episode in the group of fourth, third and second grade COPD patients vs. first grade COPD group	3.9702	1.5729-10.0211	Statistically significant
Risk of occurrence of a depression episode in the group of fourth and third grade COPD patients vs. first and second grade COPD group	8.4615	3.7771-8.9557	Statistically significant
Risk of occurrence of a depression episode in the group of fourth grade COPD patients vs. first, second and third grade COPD group	11.3043	4.1179-31.0321	Statistically significant
Risk of occurrence of a depression episode in the group of second and third grade COPD patients vs. first grade COPD group	2.9883	1.0806-8.2639	Statistically significant

that table, the relative risk of developing mood disturbances in COPD patients versus COPD-free subjects amounts to 2.7007 (95% CI 1.3167-5.5393) and is statistically significant. However, the presence of COPD was not demonstrated to be a risk factor for the occurrence of moderate or more severe depression episodes as compared with subjects without COPD. The risk of developing mood disturbances in patients with first grade COPD vs. healthy controls and in patients with second grade COPD vs. healthy controls was not significantly higher either: 0.8219 (95% CI 0.2911-2.3202) and 1.5909 (0.5794-4.3683), respectively. The relative risk in third grade COPD vs. healthy controls was 5.000 (95% CI 1.8766-13.3223) and was statistically significant, similarly to that for fourth grade COPD vs. healthy controls which was 20 (OR 20, 95% CI 6.6654-60.0112).

The risk of development of depression in second grade COPD was not significantly higher than for first grade disease severity either. However, for third and fourth grade disease the risk of depression is considerably higher than for the first grade (Table 1). Also the risk of depression in the disease more advanced than the first grade according to GOLD is higher than in subjects with first grade COPD. Similarly, it is higher for the fourth grade vs. lower grades, and for the third and fourth grades vs. lower grades (Table 1). Patients with second and third grade COPD are also at higher risk of developing depression than subjects with first grade disease.

Taking into account the smokers only, the relative risk of depression in active smokers and ex-smokers with COPD vs. healthy active smokers and ex-smokers was 1.8889, 95% CI (0.738-4.8347) and did not reach statistical significance.

The mean level of depression severity in the COPD group was 8.51 ±4.18, in the COPD-free group 7.19 ±3.67 and the difference was statistically significant (p = 0.005637). In patients with first grade disease, the mean value of scores obtained according to the Beck Depression Inventory was 7.27 ±2.83, in second grade disease – 7.58 ±4.35, in the third grade – 10.26 ±3.99, and in the fourth grade –12.57 ±5.20.

The difference between scores obtained with the Beck Depression Inventory in patients with first grade COPD

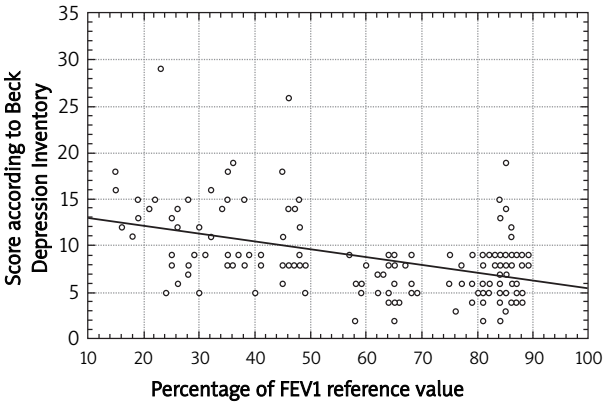

Fig. 1. Correlation between the percentage of the reference value of forced expiratory volume in one second (FEV1) and the results obtained with the Beck Depression Inventory. The correlation coefficient r = –0.466011, p < 0.001

vs. second grade COPD did not reach statistical significance ($p = 0.638530$). However, the differences in depression severity between patients with third and fourth grade COPD, and patients with first grade COPD were statistically significant: $p = 0.000028$ and $p < 0.0001$, respectively. The difference between scores obtained with the Beck Depression Inventory in patients with second grade COPD according to the GOLD criteria vs. third grade COPD was significant statistically ($p = 0.009164$) similarly to the difference between results obtained in patients with second grade COPD according to the GOLD criteria vs. those with fourth grade COPD ($p = 0.000152$). In contrast, the difference between results obtained according to the Beck Depression Inventory for third grade vs. fourth grade COPD was statistically insignificant ($p = 0.079855$). The correlation coefficient between the results obtained with the Beck Depression Inventory in the whole population of COPD patients and the value of FEV1 percentage as compared with the reference value of FEV1 was demonstrated to be negative and amount to $r = –0.466011$, $p < 0.001$.

Discussion

The results obtained in the presented study suggest that the development of COPD increases 2.7-fold the probability of developing mood disturbances. In patients with first and second grade COPD, the risk of depression does not differ significantly from the risk of depression in COPD-free subjects, whereas each subsequent grade of severity increases considerably the risk of developing a depression episode as compared with the previous grade (Table 1). As it follows from extensive meta-analysis, numerous publications emphasize marked deterioration of the quality of life as a result of COPD [15-17]. According to various studies, the onset of COPD is associated with a 3- to 9-fold increase of the risk of mood disturbances [15-17]. The severity of depression is markedly correlated with the severity according to the BODE scale in many studies [15-17]. The study by Julian *et al.* carried out in a group of 188 subjects demonstrated mood disturbances to occur in 24.5% of COPD patients [18]. In our research, this percentage amounted to 21.26%, which can be regarded as a similar result. A higher percentage of more severe depression episodes in the results of the cited Californian study is noteworthy. However, our study was not an epidemiological study carried out on a randomly selected population, hence the subjects with more severe mood disturbances may not have been treated in the Department of Pneumology. Neither were the dynamics of mood disturbances assessed, which is, undoubtedly, a shortcoming of our study. Longitudinal studies assessing the dynamics of depression in time in parallel to the course of COPD are more valuable [19]. The fact that the increased risk of depression occurs primarily in patients with third and fourth grade COPD, which is associated with burdensome symptoms, disability and life-threatening conditions, is also noteworthy [15-17].

Deteriorated quality of life, especially in third and fourth grade disease, is associated with exposure to chronic stress. The COPD-related stress is intensive and caused by the health condition, dyspnea, anxiety about the future, dependence on other people's care, as well as limitations of the patient's social activity [20, 21]. It has been demonstrated that rehabilitation in the course of COPD reduces psychological stress, thus reducing depression severity [22]. Chronic stress, undoubtedly resulting from COPD, triggers neurohormonal changes in the central nervous system – leads to hypercortisolemia [23], affects corticoliberin (CRH) release [24], raises cholesterol levels [25], blood pressure [25], causes dysfunctions of some central noradrenergic and serotoninergic transmission mechanisms [26], as well as damage to the hippocampus [26]. From the point of view of adaptation changes taking place in the process of chronic stress, a depression episode leads to an increase of CRH concentration with attenuation of the negative feedback loop in the hypothalamus – pituitary – adrenal system, corticosteroid receptor [26, 27], disturbances of serotoninergic and noradrenergic transmission [26], as well as changes at the level of cyclic AMP-responsive element binding (CREB) transcription factor [28]. The delayed action of antidepressants is probably associated with the mechanisms of their effect on CREB [29] and on tropomyosin-related kinase (Trk) receptor, as well as on brain-derived neurotrophic factor (BDNF) release [30]. Enhanced transmission on the BDNF, the Trk receptor and activation of CREB constitute probably the essence of antidepressant activity of drugs [30].

The mechanism of association between COPD and mood disturbances may also arise from the recently discovered depressogenic effect of inflammatory mediators [8, 9]. Interferons are particularly depressogenic in character [9-12]. The course of COPD is associated with systemic release of such inflammatory mediators as C-reactive protein (CRP), IL-8, IL-1β, TNF-α [4, 31], reactive oxygen species [32, 33]. Eagan *et al.* and Al-shair *et al.* demonstrated that among the investigated cytokines, only the concentration of TNF-α correlates with the onset of depression in the course of COPD [34, 35]. Tumour necrosis factor α is also responsible for depression in the course of neoplastic diseases and for the development of post-traumatic depression syndrome [36]. In another study carried out on a population of elderly COPD patients, depression was noted to correlate with body weight loss [37]. It would be interesting to check whether or not the level of TNF-α correlated with the presence and severity of depression, as well as with body mass index (BMI) in our study group. The association between inflammation and depression severity is indirectly indicated by the risk of depression increasing in parallel with the increase of severity in third and fourth grade COPD. The above phenomenon can also be explained by psychological mech-

anisms, since the level and duration of chronic stress increases with the severity of the disease. Stress and ineffective coping mechanisms lead to the phenomenon of learned helplessness, resulting in incorrect cognitive algorithms and depression [38, 39]. The susceptibility to depression depends on the individual ability to cope with stress, severity and duration of exposure to chronic stress and on the personality trait of neuroticism [40-42]. The result obtained with the Neuroticism scale indirectly correlates with the score obtained according to the Beck Depression Inventory. However, these two psychological dimensions cannot be regarded as equivalent. Therefore, measurement of all five personality traits in our patients would be interesting [40]. The neurophysiological mechanisms and the theory of learned helplessness and incorrect cognitive algorithms are probably supplementary and complementary to each other.

The fact of negative and statistically significant correlation between the percentage of FEV1 reference value and the score obtained according to the Beck Depression Inventory requires a commentary. The COPD severity grade is dependent on FEV1 value. The classification of severity grades is based on the severity of obstruction. The lower the percentage of FEV1 reference value, the more severe dyspnea, anxiety and depression, as well as quality of life impairment, which we have demonstrated in a group of patients with bronchial asthma [43, 44]. This is probably associated both with deterioration of respiratory comfort and with progression of the disease. Decrease of FEV1 value is, on the one hand, a prognostically unfavorable marker of COPD severity [45], and on the other hand, a consequence of local and systemic inflammation with secondary remodeling of the bronchial wall [46-48].

The lack of statistical significance of the difference in depression incidence among COPD patients with a positive history of nicotinism vs. healthy smokers and ex-smokers is noteworthy. This may result from the following facts:

1) the psychological profile of smokers is similar to that of COPD patients, hence the risk of developing mood disturbances is also similar [5],
2) patients with depression apply the strategy of autotherapy involving tobacco smoking – activation of the central nicotine receptor $\alpha 7$ with nicotine, which results in enhancement of motivation, improvement of mood and alleviation of disease symptoms [49],
3) smokers develop inflammation similar to the process taking place in the course of COPD, resulting in the release of the same systemic mediators as in advanced COPD [34, 35].

A study conducted on a larger cohort of subjects might demonstrate the significance of such differences as despite the lack of statistical significance the relative risk in smoking COPD patients vs. healthy smokers approximates 2.

The results of our study suggest that the group of COPD patients requires psychiatric care. Most of the patients examined by us had never been treated for mood disturbances. Indeed, the problem of mood disturbances among patients suffering from somatic diseases is still an underestimated phenomenon at the junction of clinical treatment of somatic diseases, psychiatry and clinical psychology, requiring a holistic, interdisciplinary approach [50, 51].

Conclusions

1. Development of chronic obstructive pulmonary disease increases the relative risk of a depression episode.
2. This risk increases with the increase of disease severity assessed according to the GOLD grading standard.

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