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# Chronic Obstructive Pulmonary Disease and Type 2 Diabetes Mellitus: Roflumilast And Physical Exercise in The Exacerbation Prevention.

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**ABSTRACT**

There have been examined 90 patients aged 40 to 60 years with chronic obstructive pulmonary disease and type 2 diabetes mellitus. The patients were divided into 2 groups. Group I included 45 patients who received standard pharmacologic therapy. Group II included 45 patients who received standard pharmacologic therapy in combination with roflumilast and pulmonary rehabilitation in consideration of the concomitant diabetes mellitus. In 12 months Group II participants demonstrated significant improvement in studied parameters such as number of exacerbations, symptoms (dyspnea, cough and sputum production), pro-inflammatory cytokines, anti-inflammatory cytokines, adipocytokine profile, compared to Group I. Thus, a therapy with roflumilast and pulmonary rehabilitation has provided an improvement of clinical and laboratory parameters and quality of life in patients with chronic obstructive pulmonary disease and type 2 diabetes mellitus.

**Keywords:** chronic obstructive pulmonary disease, type 2 diabetes mellitus, roflumilast, cytokines.

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## INTRODUCTION

In the past decades chronic obstructive pulmonary disease (COPD) has become one of the most common chronic lungs diseases representing a major social and medical challenge. COPD is dangerous because of its prevalence and rapid incidence rate of severe forms as well as an increase in disability and death rate [4, 6]. COPD definition by Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (GOLD, 2016) emphasizes a role of associated diseases in increasing COPD severity, their influence on quality of life, prognosis and outcomes. A COPD and type 2 diabetes mellitus (DM2) is a particularly unfavourable combination as they both develop with aging. There is clinical evidence that DM2 is associated with COPD in 2-16 % [13]. Severe exacerbations often cause COPD progression and result in frequent hospitalizations, a decrease of spirometry values and patients quality of life. All this leads to increased treatment costs, a higher rate of disability and mortality [24]. GOLD (2017) reports that COPD exacerbation management can be supported by smoking cessation, vaccination against viral and bacterial infection by patients awareness of drug therapy, accurate technique of inhalation, adequate pharmacological therapy by individual doses of long-term bronchodilators with or without inhaled corticosteroids (ICS) and phosphdiesterase-4 (PDE4) inhibitors [6]. GOLD also emphasizes non-pharmacological management of COPD exacerbations namely pulmonary rehabilitation which includes individual and group patient education, smoking cessation guidance, physical exercise and diet recommendation [7]. This paper discusses clinical efficacy of phosphdiesterase-4 (PDE4) inhibitor roflumilast and pulmonary rehabilitation devised for COPD and DM2 patients after 12 months of monitoring.

## MATERIALS AND METHODS

### Patients

There have been examined 90 patients aged from 40 to 60 years with chronic obstructive pulmonary disease and type 2 diabetes mellitus. The patients were divided into 2 groups. Group I included 45 patients with COPD and DM2: 21 female (46.7%) and 24 (53.3%) male patients with an average age of 48.58±0.87 years. Group I received standard pharmacologic therapy. Group II included 45 patients with COPD and DM2: 22 female (48.9%) and 23 male (51.1% ) patients with an average age of 47,09±0,75 years. Group II received phosphdiesterase-4 (PDE4) inhibitor roflumilast and pulmonary rehabilitation with standard pharmacologic therapy. The groups were rather similar in age ($p>0,05$), sex ($p>0,05$), sociodemographic values ($p>0,05$), therefore, they could be used for comparative assessment. COPD diagnosis was based on the integral assessment of symptoms, medical history, health status, spirometry values according to GOLD. DM2 diagnosis was made according to WHO classification (1999-2013), clinical guidance “Standards of medical care to DM patients”, clinical examination and laboratory tests. The investigation was approved by local ethics committee, and informed consent was obtained from all participants.

### Methods

A comprehensive clinical examination and laboratory tests included the following procedures:

1. Assessment of COPD severity includes the number of exacerbations for the past 12 months, the number of calls to emergency service for the past 12 months, the number of hospital admissions for the past 12 months.
2. Quantity assessment of COPD symptoms (dyspnea, cough and sputum production) by the 10-points Visual Analogue Scale (VAS).
3. Quality assessment of COPD symptoms by a modified British Medical Research Council (mMRC) questionnaire.
4. Assessment of COPD symptoms influence on patients health status by Clinical Chronic obstructive pulmonary disease (COPD) Questionnaire (CCQ).
5. Spirometry.
6. Assessment of glycated hemoglobin level (HbA1c) by biochemical serum blood test.
7. Assessment of systemic inflammation response – pro-inflammatory cytokines (interleukine (IL)-6, IL-8, tumor necrosis factor-α (TNF-α)) and anti-inflammatory cytokines (IL-4, IL-10) by enzyme-linked immunosorbent assay (ELISA) with reagents kits «INTERLEUKINE-6-ELISA-BEST», «INTERLEUKINE-8-

ELISA-BEST», «alfa-TNF-ELISA-BEST», «INTERLEUKINE-4-ELISA-BEST», «INTERLEUKINE-10-ELISA-BEST» (VEKTOR-BEST, Russia).

8. Assessment of adipocytokine profile – orexigenic hormone (leptin) and anorexigenic hormone (adiponectin) by ELISA with reagents kits «LEPTIN-Sensitive-ELISA», «ADIPONECTIN ELISA» (Mediagnost GmbH, Germany).
9. Exercise tolerance assessment by six-minute walking test.
10. Assessment of COPD influence on patients quality of life by COPD Assessment Test (CAT).
11. Quality of life assessment by The Short Form Medical Outcomes Study 36 (SF-36).
12. Quality of life assessment by St. George Respiratory Questionnaire (SGRQ).

**Pharmacotherapy**

Roflumilast (Daksas, Takeda Gmbh, Germany) was administered at 500 mcg orally once a day with sufficient amount of water for 2 months twice a year in autumn and spring.

**Pulmonary Rehabilitation**

This involved patients educational 2-weeks program: 10 practical classes of 1h 30 min each for groups of 4-5 people. Week 1 topics covered etiology, pathogenesis, symptoms, management and prevention of COPD. Week 2 covered etiology, pathogenesis, symptoms, management and prevention of DM2. All participants received books, brochures, information sheets and booklets. The patients educational program was followed by 8-weeks exercise training program. The participants were also given advice on exercise training at home.

**Statistical Analysis**

All results are presented as the mean ± SD. All data was evaluated with STATGRAPHICS 5.1 Plus for Windows. Hypothesis testing methods included one way analysis of variance (ANOVA) followed by Least Significant Difference (LSD) test. Significance level at $p<0.05$ was considered to indicate statistical significance.

## RESULTS AND DISCUSSION

A combined 12-month therapy with roflumilast and pulmonary rehabilitation in Group II demonstrated changes in the assessment parameters while standard pharmacologic therapy in Group I did not lead to statistically significant ($p > 0,05$) changes in the assessment parameters.

Group II patients with COPD and DM2 demonstrated a decrease of exacerbation events from 2,51±0,11 to 1,40±0,07 per year, i.e. in 1,8 times (F=92,83; p=0,0000), a decrease in emergency service calls from 3,17±0,12 to 1,91±0,06, i.e. in 1,6 times (F=67,82; p=0,0000), a decrease in hospital admissions from 2,04±0,09 to 1,60±0,09 per year, i.e.in 1,3 times (F=10,65; p=0,0016).

In Group II there was revealed significant improvement in subjective assessment of COPD symptoms according to 10-point Visual Analogue Scale (VAS): dyspnea – from 5.77±0.16 to 3.97±0.12, i.e. in 1.5 times (F=77.52; p=0.0000), cough – from 5.93±0.11 to 3.84±0.15, i.e. in 1.5 times (F=153.80; p=0.0000), sputum – from 3.84±0.09 to 2.20±0.08, i.e. in 1.7 times (F=90.58; p=0.0000).

Group II indicated significant improvement in dyspnea severity measured by mMRC from 2.96±0.10 to 1.98±0.09, i.e. in 1.5 times (F=54.26; p=0.0000).

CCQ results in Group II have changed in the following parameters: *Total* –from 3.99±0.72 to 2.63±0.31, i.e. in 1.36 times (F=45.78; p=0.0000), *Symptom* –from 4.15±0.48 to 3.02±0.22, i.e. in 1.13 times (F=110.21; p=0.0020), *Functional status* – from 3.84±0.31 to 2.67±0.69, i.e. in 1.17 times (F=37.23; p=0.0000), *Mental status* – from 3.48±0.36 to 2.15±0.54, i.e. in 1.33 times (F=33.19; p=0.0001).

Spirometry results were not significantly different in Groups I and Groups II ($p>0.05$).

The results of biochemical test of blood serum in Groups I and Groups II did not reveal significant difference in HbA1c level. However, it should be noted that Group II indicated a tendency to a decrease of HbA1c level from 7.51±0.08 to 7.36±0.05 % (F=3.70; p=0.0575).

Group II demonstrated a significant change in pro-inflammatory profile parameters: IL-6 – from 12.84±0.20 to 10.07±0.19 pg/ml, i.e. in 1.3 times (F=100.04; p=0.0000), IL-8 – from 13.84±0.17 to 11.26±0.30 pg/ml, i.e. in 1.2 times (F=54.21; p=0.0000) and TNF-α – from 28.60±0.22 to 23.76±0.19 pg/ml, i.e. in 1.2 times (F=281.43; p=0.0000).

Group II demonstrated a significant change anti-inflammatory profile parameters: IL-4 – from 4.06±0.14 to 6.11±0.13 pg/ml, i.e. in 1.5 times (F=107.14; p=0.0000), IL-10 – from 1.51±0.08 to 3.04±0.11 pg/ml, i.e. in 2.0 times (F=125.29; p=0.0000).

Group II revealed significant changes in adipocytokine profile parameters: leptin – from 35.64±1.23 to 28.73±1.21 mg/dl, i.e. in 1.3 times (F=67.15; p=0.0002), adiponectin – from 1.68±0.09 to 2.91±0.09 mg/ml, i.e. in 1.7 times (F=125.29; p=0.0000).

The results of a six-minute walk test in Groups I and Groups II did not reveal reliable differences (p>0.05). At the 2nd group reliable positive dynamics of CAT result was noted: from 27.11±0.35 to 21.22±0.30 (F=55.26; p=0.0000).

Group II demonstrated reliable improvement in physical and psychosocial status of life quality according to SF-36: physical functioning (PF) – in 15.38 (F=34.77; p=0.0000), role-physical functioning (RP) – in 12.06 (F=28.21; p=0.0001), bodily pain (BP) – in 16.58 (F=101.34; p=0.0000), general health (GH) – in 18.40 (F=95.67; p=0.0020), vitality (VT) – in 18.48 (F=26.11; p=0.0004), social functioning (SF) – in 13.11 (F=88.32; p=0.0003), role emotional (RE) – in 14.70 (F=65.91; p=0.0000), mental health (MH) – in 12.57 (F=65.72; p=0.0000) (Table 1).

**Table 1: SF-36 parameters on baseline and after 12 months**

| Parameters | Group I, n=45 | | Group II, n=45 | |
|---|---|---|---|---|
| | baseline | after 12 months | baseline | after 12 months |
| Physical functioning (PF) | 44.28±1.24 | 43.11±1.68 | 45.01±1.34 | 60.39±1.24* |
| Role-physical functioning (RP) | 62.44±1.34 | 60.94±1.05 | 63.18±1.15 | 75.24±1.43* |
| Bodily pain (BP) | 63.15±1.84 | 62.15±1.32 | 61.22±1.48 | 77.80±1.29* |
| General health (GH) | 40.13±1.40 | 41.11±1.66 | 39.91±1.34 | 58.31±1.65* |
| Vitality (VT) | 52.48±1.35 | 50.17±1.24 | 51.34±1.55 | 69.82±1.64* |
| Social functioning (SF) | 60.46±1.55 | 60.13±1.67 | 74.13±1.94 | 61.02±1.39* |
| Role emotional (RE) | 48.32±1.93 | 47.27±1.18 | 49.04±1.21 | 63.74±1.09* |
| Mental health (MH) | 42.44±1.25 | 40.18±1.99 | 41.54±1.27 | 54.11±1.56* |

Footnote: Group I - patients with COPD and DM2 received standard pharmacologic therapy. Group II - patients with COPD and DM2 received roflumilast and pulmonary rehabilitation with standard pharmacologic therapy. Data is presented as the mean ± SD; * – p<0.05 – differences between groups are significant.

Group II demonstrated an obvious improvement in average values of SGRQ results: symptoms – from 83.96±0.15 to 69.46±0.89 (F=67.23; p=0.0001), activity – from 81.04±0.44 to 70.14±0.23 (F=23.14; p=0.0001), impact – from 81.94±0.59 to 68.53±0.38 (F=122.71; p=0.0004), total – from 80.03±0.35 to 65.84±0.71 (F=47.01; p=0.0000).

COPD and DM2 combination has encouraged more research. The overlapping pathogenetic factors such as chronic systemic inflammation, an oxidative stress, chronic hyperglycaemia cause the development of COPD and DM2 [18, 21]. Patients with COPD and DM2 have a high exacerbation and hospitalization frequency, significant clinical symptoms of disease with low values of spirometry, higher level of leptin, low level of adiponectin, and significant insulin resistance. The treatment strategy for COPD and concomitant DM2 patients is prevention of diseases progression, decrease of significant clinical symptoms, life quality improvement, management and prevention of exacerbations and complications, reduction of mortality [9]. This strategy implementation should be supported by a reduction of risk factors influence, adequate treatment including pathogenetic, development of pulmonary rehabilitation programs in consideration with concomitant somatic pathology including educational programs, physical training [14, 19].

Although inflammatory process in COPD is complex, there are key links in its pathogenesis including PDE-4. This enzyme regulates a metabolism of cyclic adenosine monophosphate (cAMP) in pro-inflammatory and immune cells and catalyzes transition of cAMP to its inactive form – AMP [1, 22]. Roflumilast is PDE4 inhibitor that reduces activity of cells participating in the development of COPD inflammation. Therefore, in patients with COPD the level of neutrophils in sputum decreases, as well as migration of neutrophils and eosinophils in respiratory tracts [11, 20]. The results of clinical trials show high efficiency of roflumilast in decreasing of many pro-inflammatory markers, such as TNF-α, IL-1, IL-6, C-reactive protein and fibrinogen. Roflumilast is capable to prevent COPD exacerbations due to its ability to influence the neutrophils level in respiratory tract mucosa [2, 13, 17].

Patients education creates positive impact on the diseases course, its symptoms, and patients quality of life. The patients develop a larger awareness of the disease, better practical skills and compliance [3, 12, 23].
Exercise training as supportive, rehabilitation, and preventive management promotes improvement of peripheral muscles groups function and immune system function. It can also increase nonspecific protection and body resistance, as well as stimulate metabolic processes, and positively influence on cardiovascular system. Exercise training can raise patients motivation, improve their neuropsychological status, and relieve symptoms [15, 16].

Breathing exercises reduce hyperventilation and raise pulmonary ventilation as a result of separate respiration cycle phases training, normalization of inspiration and expiration volume rate, increasing of respiration depth and decreasing of respiration rate [5, 8, 10].

Thus, pathogenetic therapy with roflumilast and pulmonary rehabilitation education, exercise training for COPD and DM2 patients have resulted in evidence supported improvement of clinical and laboratory parameters. The positive results have long lasted after rehabilitation course.

## CONCLUSION

A complex therapy with PDE4 inhibitor roflumilast and pulmonary rehabilitation for patients with COPD and DM2 was developed in consideration of concomitant somatic pathology. The therapy implementation has provided an evidence-supported decrease of exacerbations, emergency services calls, and hospital readmissions. It has also resulted in a relief in COPD symptoms' severity and improvement of patients' physical and emotional health status. The complex therapy has lead to a lower dyspnea burden on health status, a decrease of systemic inflammation, an improvement of adipocytokine profile and patients quality of life.

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