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Could really systemic inflammatory markers be predictors of COPD Progression

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Abstract
Inflammatory biomarkers are considered by modern researchers as one of the best markers of effectiveness of inhaled corticosteroids (ICS) at patients with COPD, but there are a few studies about their prediction opportunity for COPD progression.
The study is devoted to study of the diagnostic value of some markers of systemic inflammation (CRP, fibrinogen, MMP-2 and -9, hyaluronic acid (HA) at patients with COPD, there role as predictors of COPD progression.
It was determined that determination of dynamic levels of such marker of systemic inflammation as MMP-2, CRP, HA can be used as parameters for further evaluation of the clinical stability of patients during their long-term follow-up.
Significant decreasing of inflammatory markers shows the adequacy of anti-inflammatory therapy of patients with COPD regardless of changes in lung function dynamic disorders.

Keywords: chronic obstructive pulmonary disease, systemic inflammation, predictors, biomarkers.

Introduction
Chronic obstructive pulmonary disease (COPD) progression is variable. Some patients have a relatively stable course, while others suffer relentless progression leading to severe breathlessness, frequent acute exacerbations of COPD (AECOPD), respiratory failure and death [7].
There are many studies in which inflammatory biomarkers have been used in an attempt to predict future exacerbations and progression; it is likely that these biomarkers represent a consequence rather than the cause [6].
The purpose of major modern researches is to examine if COPD phenotypes and systemic inflammatory markers predict the risk for COPD exacerbations, defined as requiring treatment with either systemic steroids or antibiotics [10]. For examples recent studies show that COPD patients exhibit low-grade systemic inflammation, and that plasma fibrinogen and high neutrophil counts are related to faster declines in lung function [8, 10]. It was established that high serum C-reactive protein (CRP) and matrix metalloproteinase (MMP)-9 levels were related to FEV_1 decline.
But most of studies try to predict not progression in general but time to the next exacerbation [6, 7]. Inflammatory biomarkers are considered by modern researchers as one of the best markers of effectiveness of inhaled corticosteroids (ICS) in COPD patients, but there are a few studies about their prediction opportunity for COPD progression.
The aim of our study was to establish the diagnostic value of some markers of systemic inflammation (CRP, fibrinogen, MMP-2 and -9, hyaluronic acid (HA)) in COPD patients as predictors of COPD progression.
Materials and methods. 50 COPD patients (age – 62,1±0,91 years) formed a main group, which was divided into subgroups according to the FEV_1 level: subgroup 1 – 25 patients (age – 61,8±1,60 years, men – 24 (96,0%)) with GOLD II, subgroup 2 – 25 patients (age – 66,2±1,28 years, men – 24 (96,0%)) with GOLD III. All patients accepted therapy (bronchodilators (BD) or ICS according to the stage of disease) variably.
Analyses of complaints, disease histories, clinical and functional examination, markers' levels, adjusted patients' drug therapy were done at visit 1. On this visit basic treatment was prescribed to patients: patients of subgroup 1 used basic treatment with long acting muscarinic agonists (LAMA) once daily, patients of subgroup 2 – with ICS and long acting beta-agonists (LABA) twice a day.
Than all patients visited us every three months in the following way: visit 2 – in 3 months, visit 3 – in 6 months, visit 4 – in 9 months after correction of the treatment.

The control group consisted of 26 healthy persons (age-58,9±11,5 years, men – 18 (69,2%).
Methods included clinical data, spirometry, plasma levels of CRP, fibrinogen MMP-2 and -9, HA.
COPD diagnoses were formulated and basic treatment was prescribed in compliance with the recommendations of the Order of the Ministry of Healthcare of Ukraine №555 from 27 June 2013 [2].
The research of the external respiration function (ERF) with a characteristic of the main bronchial obstruction indicators (forced vital capacity of lungs (FVCL), pulmonary forced expiratory volume in 1 minute (FEV_1) was conducted using computer spirograph "Master Screen Body/Diff" ("Jager", Germany). The reversibility test was made using 400 mcg of salbutamol.
CRP level in blood plasma was determined by quantitative immunological method [3]. The levels of MMP-2 and -9 in plasma were determined by ELISA [9]. The level of fibrinogen in the blood plasma was determined by Clauss method [4]. The level of HA in plasma was determined by a modified ELISA Gold 5].
Statistical methods were conducted by biometric analysis implemented in the EXCEL-2003 (№ 74017-641-9475201-57075), STATISTICA 6.0 (№ 31415926535897) program packages [1].

Results. All the 50 patients were involved in the research in stable phase of COPD. On the stages of long-term dynamic follow-up (when making further visits with biomarkers levels identification) none of the patients revealed any clinical signs of infective exacerbation of the disease. Not a single patient was excluded from the study.
On visit 1 in subgroup 1 mean FEV_1(post) was 67,7±1,65% pred., in subgroup 2 – 37,5±1,61% pred.
In general levels of inflammatory markers in COPD patients on visit 1 were significantly higher than in control group (table 1), but in subgroups they were almost identical.

Table 1: Dynamic of biomarkers of patients with COPD

Parameter	Main group				Control group
	visit 1	visit 2	visit 3	visit 4	
C-RP, mg/l	9,2±0,91*	7,8±0,55	7,1±0,43	6,4±0,34	6,25±0,14
fibrinogen, g/l	3,1±0,10*	3,0±0,09*	2,9±0,09*	2,6±0,09*	2,85±0,17
MMP-2, cu	131,5±6,58*	126,3±5,28*	125,1±3,99*	100,0±2,96	92,5±4,10
MMP-9, cu	171,1±13,10*	143,0±7,74*	138,4±8,36*	109,5±3,20	103,1±5,55
HA, mg/ml	0,28±0,01*	0,23±0,01*	0,20±0,01	0,13±0,01	0,15±0,02

Note. * – $p<0,05$ with control group

In a year it was progressively aggravation of disease in 9 (18,0%) COPD patients (8 patients from subgroup 1 and 1 patient from subgroup 2), which was accompanied with decreasing of FEV_1. Corresponding to dynamic of FEV_1 patients of subgroup 1 were divided into 2 cohorts: subgroup 1A – with improvement of FEV_1, subgroup 1B – with decreasing of FEV_1 (table 2).

Table 2: Dynamic level of FEV_1 in COPD patients

Subgroups	n	FEV_1 (post), % pred.		p by Wilcoxon
		visit 1	visit 4	
1	25	67,7±1,65	71,1±2,15	0,110
1A	17	66,7±1,54	76,0±1,25	0,000
1B	8	69,8±3,60	60,8±4,28	0,013
2	25	37,5±1,61	50,1±2,23	0,000

The results showed that the level of CRP was significantly decreased in the subgroup 1A after 1 year of systemic administration of appropriate therapy, in the subgroup 1B it was almost unchanged; levels of other markers of systemic inflammation decreased in the both subgroups 1A and 1B, i.e. regardless of the FEV_1 dynamics (table 3).
In the subgroup 2 after 1 year of adequate therapy parameters of systemic inflammation markers was significantly decreased (table 3). Thus, the results indicate that during adequate therapy the severity of systemic inflammation is greatly reduced at COPD patients of both GOLD II and GOLD III regardless of changes in lung function dynamic disorders.

Conclusions

1. Determination of dynamic levels of such marker of systemic inflammation as MMP-2, CRP, HA can be used as parameters for further evaluation of the clinical stability of patients during their long-term follow-up.
2. Significant decreasing of inflammatory markers shows the adequacy of anti-inflammatory therapy of patients with COPD regardless of changes in lung function dynamic disorders.

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