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Peculiarities of Response of Systemic Inflammation Markers In Patients With Chronic Obstructive Pulmonary Disease Under Their Long-Term Follow-Up

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Systemic inflammation is one of the links of pathogenesis of chronic obstructive pulmonary disease (COPD). However, the role of numerous molecular markers in various categories of patients, in phases of pathological process, depending on the presence and degree of microbial load, etc. is being currently defined and specified.
It is determined that a certain part of patients with COPD (regardless of the stage), even with stable course of the diseases, may reveal increased levels of systemic inflammation markers, particularly levels of CRP and Fibrinogen, which reflect the processes of activation of chronic systemic inflammation in these very patients. The most frequent and the most marked chronic systemic inflammation is found in patients with severe course of COPD, which requires identification of such category of patients in order to minimize the risk of systemic effects formation in these patients. Sometimes, increase in the CRP and/or Fibrinogen levels in the blood plasma of patients with COPD may witness to insufficient glucocorticosteroid medication and require therapy adjustment.

Keyword: chronic obstructive pulmonary disease, systemic inflammation, pulmonary fibrosis, long-term dynamic.

1. Introduction

The concept of systemic inflammatory response (or systemic inflammation) in the pathogenesis of chronic obstructive pulmonary disease (COPD) is relatively new, that is why the attention of pulmonologists is concentrated on a search for the most informative markers of the severity of inflammation depending on the stage of the disease, phase of pathological process, presence in patients' of comorbid diseases etc. [3, 14]. The issues concerning diagnostic significance of such biomarkers as C-reactive protein (CRP), Fibrinogen, proinflammatory interleukins 1, 6 and 8, tumor-necrosis factor-α etc. are being actively explored nowadays [8, 11].

Thus, CRP is considered a marker of an acute phase of the inflammation, as its level quickly grows with the tissue injury. Under COPD exacerbation, the protein level in the patients' blood plasma may grow up to 40–100 mg/l, and sometimes to 200 mg/l (with a generally accepted normal index being up to 10 mg/l) [10, 13].

Fibrinogen, which precedes fibrin synthesis in the blood coagulation cascade, is also considered a protein of the acute phase of the inflammation. It is proved that under COPD it may intensify proinflammatory effects of other molecular factors in the focus of inflammation [6, 9].

However, accurate mechanisms of the chronic systemic inflammation development under COPD are currently studied on an insufficient level.

Due to the aforementioned, the aim of our work was to identify diagnostic significance of the CRP and Fibrinogen plasma levels in patients with COPD under their long-term dynamic follow-up.

2. Research Materials and Methods

We have conducted a prospective study which involved 48 patients with COPD (men – 46 (95.8%), women – 2 (4.2%); average age – (60.4 ± 1.4) years) under their dynamic follow-up within 9 months.

At first, all patients went through a screening (visit-1), during which we assessed their complaints, disease histories, conducted clinical and functional examination, identified the CRP and Fibrinogen levels as well as adjusted patients' drug therapy. Further on, every three months we visited the patients in the following way: visit-2 – in 3 months, visit-3 – in 6 months, visit-4 – 9 months after their involvement in research.

The obtained results were analyzed retrospectively after completion of all stages of the research by all patients.

The COPD clinical diagnoses were formulated in compliance with the recommendations of the Order of the Ministry of Healthcare of Ukraine №128 from 19.03.2007 [2].

All the examined people gave their consent to clinical research.

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 spirometry with the help of the Master Screen Body/Diff device ("Jager", Germany). The post-bronchodilator test of bronchial obstruction reversibility was made using 400 mkg of salbutamol.

The CRP level in the patients' blood plasma was identified using the immunoturbidimetric method with the help of the automatic analyzer «Cobas e411» (Roche Diagnostics GmbH) [5, 12]. The results were compared with the generally accepted norm (up to 10 mg/l).

The Fibrinogen level in citrated plasma was identified using the modified Clauss method with the help of the automatic analyzer «Cobas e411» (Roche Diagnostics GmbH) [6, 7]. The results were compared with the generally accepted norm (1.50 – 3.75 g/l).

Statistical treatment of the research materials was conducted using the methods of biometric analysis implemented in the EXCEL-2003 (№ 74017-641-9475201-57075), STATISTICA 6.0 (№ 31415926535897) program packages [1].

3. Results and Discussion

All the 48 patients were involved in the research in the phase of stability of the pathological process; none of them demonstrated any clinical signs of infective exacerbation 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, either. Not a single patient was excluded from the research on its various stages for any reason.

The retrospective analysis of the obtained research results showed that on the whole, the CRP and Fibrinogen levels in patients with COPD did not correlate with each other ($r=0.11$; $p>0.05$).

Among the examined patients we found those who did not have increased CRP and/or Fibrinogen levels either on the screening stage (visit-1) or during the further visits as well as those having increased levels of either CRP of Fibrinogen, or both markers simultaneously at least on one of the visits, including the screening one. However, if under increase of the CRP levels comparing to normal indexes the former did not correlate with the Fibrinogen levels ($r=0.22$; $p>0.05$), under increase of the Fibrinogen levels the latter correlated with the CRP levels, the correlative relation being direct and of medium power ($r=0.45$; $p<0.05$).

It is most likely that CRP is a more responsive marker and is able to reflect changes in patient condition since before the other inflammatory marker, particularly Fibrinogen, starts to respond in this situation.

Based on the elicited data, we set the following objective: to determine whether the degree of bronchial obstruction could influence the response of systemic inflammation markers in patients with COPD in the stable phase of the disease and what it was most likely to have

related to. In order to solve this objective, the examined patients were split into two groups: group 1 was composed of 26 (54.2%) patients with mild course of COPD (stages I and II), whose level of post-bronchodilator FEV_1 exceeded 50% of the appropriate number; group 2 was composed of 22 (45.8%) patients with severe course of COPD (stages III and IV), whose level of post-bronchodilator FEV_1 made less than 50% of the appropriate number.

The analysis revealed that under mild course of COPD (group 1), only 4 (15.4%) people demonstrated permanent increase in the levels of inflammatory markers, while under severe course of the disease (group 2), the levels of inflammatory markers would increase on this or that stage of follow-up in nearly half the patients (in 45.5%). Coming out of the aforementioned, for the further detailed analysis, the patients from each of the groups were further divided into two respective subgroups; herewith, subgroups with increased levels of this or that inflammatory marker came forth: subgroup 1 – group 1 patients with permanent increase in the CRP and/or Fibrinogen levels; subgroup 2 – group 2 patients with permanent increase in the CRP and/or Fibrinogen levels (Graph 1).

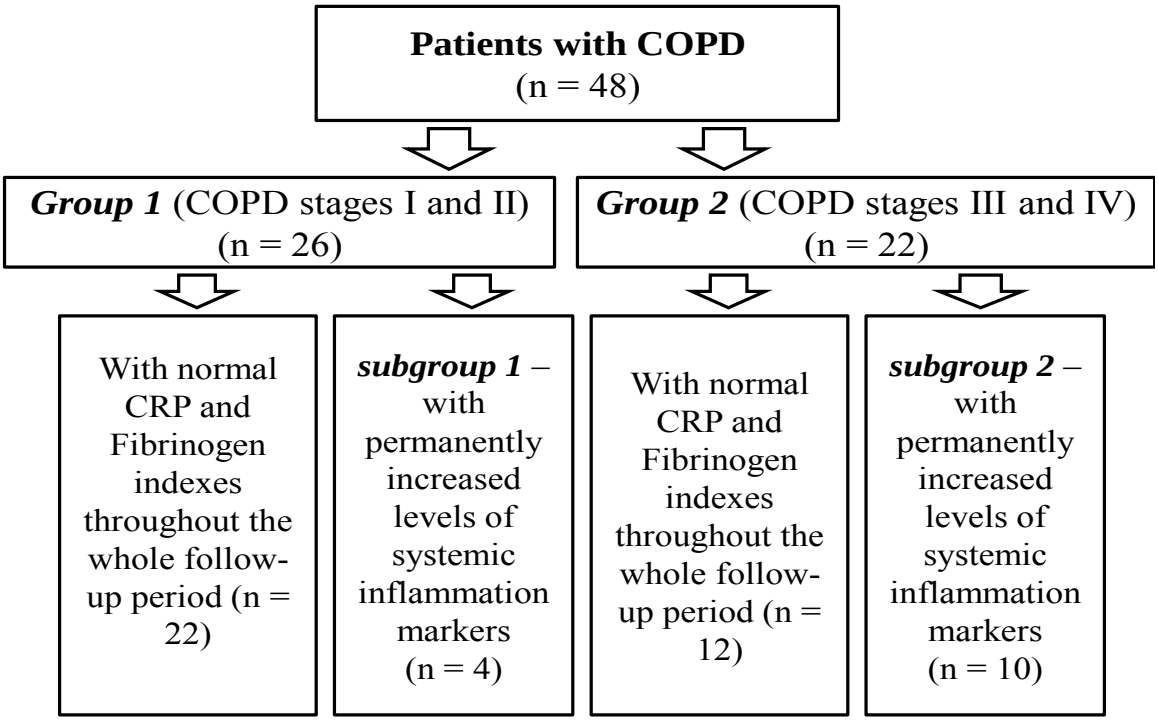

Fig 1: Group and subgroup division of the examined patients with COPD

The individual analysis revealed that on the screening stage (visit-1), the majority of the patients from subgroup 1 (3 out of 4 people) demonstrated increase in the Fibrinogen level only (maximum – 4.5 g/l). Under the further follow-up of these patients, in two of them the marker level came back to normal number as early as next visit (3 months after their involvement in the research) and did not increase any longer throughout the whole follow-up period; in one patient, the marker level normalized on visit-3 (6 months after their involvement in the research). One more patient, whose level of Fibrinogen was normal on the screening visit, demonstrated its slight increase on visits-2 and -3 (4.0 and 3.9 g/l respectively; however, no clinical signs of infective

exacerbation of COPD were detected) and coming back to normal numbers on visit-4.

On the screening visit, the patients from subgroup 2 demonstrated increase in the CRP level and/or the Fibrinogen level; moreover, if the CRP level exceeded normal indexes in 7 out of 10 people on this visit (maximum – 36.9 mg/l), the Fibrinogen level exceeded normal indexes only in 4 people out of 10 (maximum – 4,7 g/l). Further on, after drug therapy adjustment (and these very patients necessitated therapy adjustment, which had been made on the screening stage, as 6 of them did not take inhaled glucocorticosteroids they had to take based on a stage of the disease and 4 of them took medications in inadequate doses), only three patients had the CRP level slightly increased on visit-2 (10.7, 15.6 and 24.5 mg/l) and two of them had the CRP level slightly increased on visits-3 (16.7 and 24.7 mg/l) and -4 (12.6 and 17.0 mg/l).

The Fibrinogen level permanently increased in 6 patients of this subgroup (maximum – 4.8 g/l).

Thus, under more morked bronchial obstruction in patients with COPD as well as with inadequate drug therapy under severe course of the disease (particularly, concerning glucocorticosteroid therapy) it is possible to observe more frequent formation and more marked manifestation of chronic systemic inflammation, which is a basis for systemic effects development in this specific category of patients.

4. Conclusions

The conducted work led us to the following conclusions:

1. A certain part of patients with COPD (regardless of the stage), even with stable course of the diseases, may reveal increased levels of systemic inflammation markers, particularly levels of CRP and Fibrinogen, which reflect the processes of activation of chronic systemic inflammation in these very patients.
2. The most frequent and the most marked chronic systemic inflammation is found in patients with severe course ofCOPD, which requires identification of such category of patients in order to minimize the risk of systemic effects formation in these patients.
3. Sometimes, increase in the CRP and/or Fibrinogen levels in the blood plasma of patients with COPD may witness to insufficient glucocorticosteroid medication and require therapy adjustment.

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