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Diagnostic and Prognostic value of Hyaluronic acid at patients with COPD

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Abstract
Chronic inflammation and airway remodeling are characteristics of chronic obstructive pulmonary disease (COPD). Abnormalities in hyaluronic acid, a component of the extracellular matrix, may be involved in the pathogenesis of COPD. But there are no researchers about its role like a marker of effectiveness of anti-inflammatory therapy (AIT) at patients with COPD.
The study is devoted to the diagnostic value of HA at patients with COPD, the role of the HA as a marker of the effectiveness of AIT at patients with COPD.
It was determined that the level of HA at patients with COPD before AIT was significantly higher than it at patients of the control group. But in 3 months after correction of treatment the level of HA decreased significantly at all patients comparing to previous visit, which corresponded to the level of the control group.
It means that the significant decreasing of HA level at patients with COPD may be a marker of the effectiveness of AIT.

Keywords: chronic obstructive pulmonary disease, systemic inflammation, pulmonary fibrosis, hyaluronic acid.

1. Introduction
Hyaluronic acid (HA) (also called haluronan or hyaluronate) is an anionic, nonsulfated glycosaminoglycan (GAG) distributed widely throughout connective, epithelial, and neural tissues [1].
Abnormalities in hyaluronic acid, a component of the extracellular matrix, may be involved in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD), in vitro research indicates [2]. Chronic inflammation and airway remodelling are characteristics of COPD [3].
The study, conducted by an international research team, focused on the expression of glycosaminoglycans (GAGs) and their metabolizing enzymes in primary human airway smooth muscle cells (ASMC) [4]. GAGs are essential constituents of the extracellular matrix in the lung and play a key role in regulating tissue flexibility [2].
Other research indicate a relationship between HA levels, local inflammation and severity of disease, and suggest enhanced breakdown of HA in the lungs of patients with COPD. HA is an extracellular matrix compound with proinflammatory activity [4]. HA levels in induced sputum from patients with COPD were measured and related to local inflammation. HA levels were significantly higher in the sputum from patients with COPD than controls [5, 6].
That is why HA is considered by modern researchers as one of the markers of inflammation at COPD, but there are no researchers about its role like a marker of effectiveness of anti-inflammatory therapy (AIT) at patients with COPD.
That is why **the aim** was to study the diagnostic value of HA at patients with COPD, the role of the HA as a marker of the effectiveness of AIT at patients with COPD.

2. Materials and methods
We have conducted a prospective study which involved 74 patients with COPD (of II and III stage), which formed a main group (age – 62,1±0,91 years old: men – 68 (91,9%)), which are either accepted therapy variably or did not take AIT which should be taken according to the stage of disease.
At first, all patients went through a screening (visit 1) (n=74), during which we assessed their complaints, disease histories, conducted clinical and functional examination, identified the HA level as well as adjusted patients' drug therapy.
Depending on the degree of bronchial obstruction (BO) patients of the group were divided

into two subgroups: subgroup 1 – patients with mild COPD course (I and II stage of disease) Which, according to national and international guidelines do not require continuous use of inhaled glucocorticosteroids (IGCC); subgroup 2 – patients who had severe course of COPD (III and IV stage of disease which require continuous use of IGCC.

Further the most part from the patients of the main group (50 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 their involvement in research after correction of the treatment. These patients make main group of dynamic observation.

The control group consisted of 26 healthy individuals (age – 53,2±2,8 years old).

Methods included general studies, spirometry, plasma levels of HA prior the basic treatment and during basic therapy.

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 [7].

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 level of HA in plasma was determined by a modified ELISA Gold [8]. The total amount of GAGs was assessed by optical density of the solution containing the complex formed by these polysaccharides with alcyan blue. An important feature of the above, the dye is that, depending on the acidity of the medium it selectively forms complexes with sulfated (acidic environment) or nonsulfated (alkaline) GAGs. We used monochromatic light with a wavelength of 480-492 nm. As calibration standards used highly clean HA («Sigma», USA).

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 [9].

All the examined people gave their consent to clinical research.

3. Results

All the 74 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.

On visit 1we found that the level of HA at patients of main group was significantly higher than it at patients of the control group (Table 1), being increased almost twofold, but in subgroups of patients depending on the severity of the disease were almost identical.

Correlations between the HA and the severity of the disease has not been determined (r = -0,109; p = 0.355), while direct correlation was determined between the level of HA and FEV_1 (post) (Fig. 1).

Table 1: HA levels in plasma of patients with COPD on visit 1

Groups and subgroups	HA, mg/ml		p
	M±m	Mediana	
Main group (n=74)	0,27±0,01	0,24	P_{m-c}=0,000
subgroup 1 (n=37)	0,28±0,01	0,25	p_{1-c}=0,000
subgroup 2 (n=37)	0,26±0,01	0,23	p_{2-c}=0,000 p_{2-1}=0,235
Control group (n=26)	0,15±0,02	0,13	

Notes: 1. m – main group;
2. c – Control group;
3. 1, 2 – appropriate subgroups.

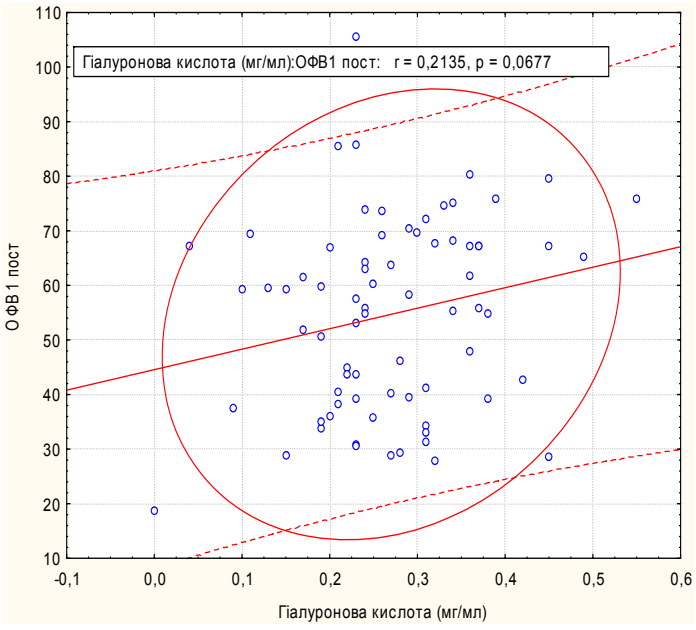

Fig 1: Dispersion the HA values in plasma at COPD patients depending on the level of FEV_1 (post)

Further observation from one visit to another shows gradually decreasing of HA level at patient of main dynamic group (p_{v2-v1} = 0,000; p_{v3-B2} = 0,000; p_{v4-B3} = 0,001; p_{v4-B1} = 0,000 by Wilcoxon criterion). In a year of regular treatment the level of HA was adequate to the control group (Table 2).

Table 2: HA levels in plasma of patients with COPD during their dynamic observations

Groups and subgroups	HA, mg/ml				p
	visit 1	visit 2	visit 3	visit 4	
Main group of dynamic observation (n=50)	0,28±0,01	0,23±0,01	0,20±0,01	0,13±0,01	P_{v1-c}=0,000 P_{v2-c}=0,001 P_{v3-c}=0,036 P_{v4-c}=0,388
subgroup 1d (n=23)	0,29±0,01	0,25±0,01	0,21±0,01	0,13±0,01	p_{v1-c}=0,000 p_{v2-c}=0,000 p_{v3-c}=0,001 p_{v4-c}=0,436
subgroup 2d (n=27)	0,27±0,01	0,22±0,01	0,20±0,01	0,13±0,01	P_{v1-c}=0,000 p_{v2-c}=0,007 p_{v3-c}=0,039 p_{v4-c}=0,415
Control group (n=26)	0,15±0,02				

Notes: 1. m – main group;
2. c – Control group;
3. 1, 2 – appropriate subgroups.

In the subgroup of patients was similar dynamic parameter (Table 2), while for the subgroup 1d statistical parameters were p_{v2-v1}=0,002; p_{v3-v2} =0,000; p_{v4-v3}=0,001; p_{v4-v1}=0,000 by Wilcoxon criterion, and for the subgroup 2d they were p_{v2-v1}=0,000; p_{v3-v2}=0,004; p_{v4-v3}=0,000; p_{v4-v1}=0,000 by Wilcoxon criterion.

Individual analysis showed that among patients of subgroups 1d on visit 1 only three patients had HA level below 0,20 mg/ml, on visit 2 – five patients, on visit 3 – eight patients, on visit 4 (after a year of adequate drug therapy) – 20 persons.

Thus, as a result of our study, diagnostic and prognostic significance of such marker of systemic inflammation as HA levels can be used for individual assessment of COPD patients on stages of their long observations, and assist the physician in evaluating the adequacy of the medical treatment of the patient.

4. Conclusions

1. Determination of levels of such marker of systemic like HA can be used as parameters for further evaluation of the clinical stability of patients during their long-term follow-up.
2. The significant decreasing of HA level at patients with COPD may be a marker of the effectiveness of AIT.

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