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Dynamics of systemic inflammatory markers in case of exacerbation of COPD (III degree of bronchial obstruction) in overweight patients with the optimization of management and treatment

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Abstract

Management of patients with chronic obstructive pulmonary disease is the prerogative not only of pulmonologists, but also of physicians and family doctors. This problem still remains the most common chronic human disease, which is widespread in both developed and developing countries due to its high prevalence, progressive course, and reduced life expectancy of patients. The risk of COPD development, especially in the elderly, may be attributed to socio-economic causes and low living standards, and at the same time its incidence and severity of the course and its prognosis are often determined by the influence of concomitant pathology on the frequency of exacerbations, so the problem of comorbidity is becoming increasingly important. The objective of this study was to determine the diagnostic significance of serum levels of CRP, TNF- α and leptin in exacerbation phase of COPD (III degree of bronchial obstruction) in overweight patients in order to optimize management and treatment strategies. The study involved the examination of 45 overweight patients: 18 of them were in the phase of remission; 27 overweight patients were in the phase of exacerbation of the pathology, and were in turn divided into 2 subgroups: patients of subgroup I (n = 15) were administered xanthine only, and patients of subgroup II (n = 12) have also agreed to modify their life style. The research findings showed a decrease in all the studied indices on the 10th day. Data obtained after three months of treatment were more significant, especially in patients of subgroup II. Thus, overweight has a negative influence on the course of COPD (III degree of bronchial obstruction), and the use of comprehensive therapy with xanthine and lifestyle modifications in the treatment of this pathology improves clinical symptomatology and has a positive effect on the indices of inflammatory activity, which was manifested by a significant decrease in CRP, TNF- α , and leptin levels and contributed to the improvement of their quality of life.

Keywords: COPD, overweight, CRP, TNF- α , leptin

Introduction

Findings of WHO experts show that chronic obstructive pulmonary disease (COPD) is one of the most common chronic human diseases [8, 13]. This pathology is still inadequately diagnosed worldwide, and is associated with high mortality rates and is a significant burden for the health care system. [Feshchenko Yu. I., 2020] [2, 4]. The majority of authors state that the disease has become significantly "younger", and the direct and supplementary social costs for treatment are on an increase annually [3, 12]. The risk of COPD development, especially in the elderly, is attributed to significant socio-economic costs and low living standards, meanwhile its incidence rate is associated with the impairment of general and local adaptive defense mechanisms. Respiratory disease experts around the world have observed the lack of efficacy of available approaches to the diagnosis, treatment and rehabilitation of patients with this pathology [2, 4, 5].

The obtained literature data proved that COPD develops in several stages. The disease begins with edema, hypersecretion of mucus, changes in the rheological characteristics of bronchial secretion (its viscosity and adhesiveness increase, while its elasticity decreases), which contributes to the impairment of mucociliary clearance [1, 7, 15], mucostasis, and hence the development of microbial colonization with the development of inflammatory process in the bronchi. The development and progression of the inflammatory process in COPD is generally determined by immune status [1, 4], as the leading role belongs to the changes in the system of bronchopulmonary defense and immune responsiveness of the body. This results in the impairment of the processes of cooperation of T- and B-lymphocytes system, and suppression

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of cellular and humoral immunity [4, 6].

Recently, more and more attention is paid to the study of various phenotypes of chronic obstructive pulmonary disease, in particular and in combination with overweight, which is a well-studied risk factor for the development and rapid progression of a number of chronic diseases, including pathology of the upper and lower respiratory tract. (Şahin HD 2017, Naz İ 2017, Varol Y 2017). The role of overweight in the development and rapid progression of respiratory pathology may be proved by the fact that weight loss leads to the decrease in the clinical manifestations of COPD [10, 11].

It has been established that the prevalence rates of chronic obstructive pulmonary disease and overweight increase quite rapidly all over the world. According to the data of analysis and systematic review made in 28 countries, the prevalence rates of chronic obstructive pulmonary disease among the adult population is approximately 10% (Yu.I. Feshchenko *et al.*, 2018) [2, 4]. According to the world data, more than 30% of the world's population is overweight, among them: 16.8% – women, 14% – men. In Ukraine it is 30% of the adult population (in most European countries – 9-20%). At the same time, global prognoses show that nearly 700 million adults will have suffered from overweight by 2020. According to the WHO, normal body mass index may vary within the range of (18.5-24.9) kg/m², while BMI within the range of (25.0-29.9) kg/m² should be regarded as overweight [3, 9, 16]. Possible mechanism of weight gain, with parallel loss of muscle mass among COPD patients, may be associated with the decrease in physical activity due to shortness of breath during exercises, as well as the long-term use of systemic glucocorticosteroids with the development of immunosuppressive effects at the late stages of the disease. Thus, the role of overweight in the development and rapid progression of respiratory pathology can be proved by the fact that weight loss reduces the degree of clinical manifestations [4, 6, 17]. It is a proven fact that overweight is accompanied by inflammation of adipose tissue, which progresses with its infiltration by immunocompetent cells. Since the inflammatory reaction occurs in the tissue, which is well vascularized and innervated, therefore the systemic manifestations should be expected [1, 10, 14].

The course, duration and progression of the disease are determined not only by an increase or decrease in the level, but also by the correlation of pro- and anti-inflammatory cytokines, which provide the sequence and completeness of the immune response, carry out a short-term regulation of intercellular interactions of all parts of the immune system, which affects the severity of the immune response to damage in the development of chronic inflammatory reactions, systemic inflammatory response syndrome [1, 12, 15].

A number of scientific studies have been carried out in Ukraine and other countries in order to study the role of pro-inflammatory cytokines in the formation and course of COPD. For instance, we are familiar with the studies which demonstrate the importance of these indices as being the predictive markers of COPD in patients with arterial hypertension, associated with overweight (Sytnyk K.O., 2012) and bronchial asthma in combination with obesity (Halamba A.A., 2016). However, the issue of the role of pro-inflammatory cytokines in the process of generalization of the inflammatory response with the decrease of FEV₁ levels below 50% in overweight patients still remains unclear [10, 11, 12].

The objective of the study was to determine the diagnostic

significance of serum levels of CRP, TNF- α and leptin in exacerbation phase of COPD in overweight patients in order to optimize management and treatment strategies.

Materials and Methods

The verification of the diagnosis of COPD and its formulation were carried out in accordance with the Order of the Ministry of Health of Ukraine №555 from June 27, 2013 “On approval and implementation of medical-technological documents on standardization of medical care in chronic obstructive pulmonary disease”. Patients being in a stable phase of the process received baseline therapy in accordance with the currently valid order of the Ministry of Health of Ukraine №555 from June 27, 2013, which involved the use of long-acting bronchodilators, inhalational and/or systemic glucocorticosteroids, and short-acting bronchodilators, if necessary [14].

Complex therapy of patients with exacerbation of COPD (III degree of bronchoconstriction) was carried out according to the schedules covered in the order of the Ministry of Health of Ukraine №555 from June 27, 2013. It was aimed at the elimination of inflammatory process in bronchi (glucocorticosteroid nebulations, administration of high-doses of inhalational glucocorticosteroids with preference to their combinations with prolonged action beta-2-agonists (fluticasone + salmeterol, budesonide + formoterol), and systemic glucocorticosteroids if necessary); restoration of adequate ventilation (inhalational short-acting and long-acting β_2 agonists: salbutamol sulfate, fenoterol hydrobromide, salmeterol, formoterol fumarate, with preference given to nebulization with the combination of short-acting β_2 agonists and cholinolytics (ipratropium bromide + fenoterol hydrobromide), if treatment with inhalational bronchodilators failed, prolonged oral administration of theophylline or intravenous eufhylline by drop infusion were used); restoration of mucociliary clearance (ambroxol, acetylcysteine), elimination of the etiological factor of exacerbation.

In case of infectious exacerbation of COPD (III degree of bronchoconstriction), the initial antibacterial therapy was of an empirical character, predominantly involving the administration of oral antibacterial drugs: aminopenicillins, inhibitor-protected aminopenicillins or macrolides, if necessary (ineffectiveness of therapy, allergic reactions) – respiratory fluoroquinolones were used.

To determine the dynamics of the inflammatory response, we examined 45 overweight patients: 18 of them were in the phase of remission; 27 patients with overweight were in the exacerbation phase of the pathology, and in addition to basic therapy, they received xanthine at a dose of 5 ml/kg of body weight, administered intravenously three times a day for 7 days. On the background of COPD treatment, the patients were offered a comprehensive therapy with lifestyle modifications, which involved learning about the condition, dietary intervention and regular exercises for three months. Thus, the patients agreed to be distributed into several subgroups, namely: patients of subgroup I (n = 15) received xanthine medication only and patients of subgroup II (n=12) also agreed to modify their lifestyle. Drug treatment of COPD exacerbation was carried out until we noticed the improvement in their condition, namely the reduction of shortness of breath, cough, expectorations, reduction of dry rales and a significant improvement of general health status and clinical-laboratory markers. The control group included

12 overweight apparently healthy individuals (AHI) representative by sex and age, without any signs of pulmonary diseases or other pathologies of internal organs. Patients' condition, clinical, functional and laboratory markers, as well as the dynamics of CRP, TNF- α and leptin levels were evaluated on day 10 and 3 months after the treatment. Computed spirometry with the help of "SpiroCom medic" (KhAI, Kharkiv, Ukraine) was used to study the indices of respiratory function with indicators of main bronchoobstructive indices (forced vital capacity (FVC) of lungs, forced expiratory volume (FEV1)).

The levels of systemic inflammatory markers were determined in blood serum. The TNF- α levels were identified using ELISA kits (Dialcone, France), the serum CRP level was determined by a semi-quantitative latex agglutination method using the Dialab reagent kit (Austria), and the leptin level was identified using «DRG Leptin ELISA» kit (Germany).

Copyright software applications, based on Microsoft Excel software (rating, margin of errors, t-test), were developed for statistical processing of the study material at all stages of the research work. Some of the data development tasks were performed using licensed Microsoft Excel statistical analysis

software, including programs for descriptive statistics and graphic presentation. The reliability of the obtained indicators was confirmed by calculating the margin of error ($\pm m$) for relative values according to the commonly-known formula.

The probability of data significant differences in the compared groups, taking into account a large number of observations and proximity to normal distribution, was proved by calculating the Student's t-distribution values and determining the accuracy of the prediction error (p). The difference was considered to be significant at $P < 0.05$. Calculation of pair factorial correlation coefficient was carried out together with the Pearson's (r) calculation.

Research findings and their discussion

Assessing the indices of respiratory function (RF), we have observed that in overweight patients in the phase of exacerbation, the rates of FEV1 were 2.4 times lower ($p2 < 0.001$), the rates of FVC – 1.3 times lower ($p2 < 0.001$), and FEV1/FVC – 1.5 times lower ($p2 < 0.001$) as compared to the indices observed in the group of apparently healthy individuals (AHI), and 1.2 times, 1.1 times and 1.1 times lower ($p1 < 0.001$) than the same indicators in the remission phase (table 1).

Table 1: Indices of respiratory function (%) in overweight COPD patients with III degree of bronchial obstruction in different phases of the pathologic process, ($M \pm m$)

Indices in subgroups of examined patients	Apparently healthy individuals with excessive body weight n = 12	Main study group, n = 45		p_1	p_2
		Remission phase n = 18	Exacerbation phase n = 27		
FEV1 (%)	81.90 \pm 5.20	41.24 \pm 1.27	33.87 \pm 0.96	<0.001	<0.001
FVC (%)	79.10 \pm 4.40	68.25 \pm 0.96	62.56 \pm 0.83	<0.001	<0.01
FEV1/FVC	78.70 \pm 5.20	55.24 \pm 1.21	53.43 \pm 0.61	<0.001	<0.001

Notes:

1. p_1 – Significant difference between the indices observed in patients from the main study group in the phase of remission and the phase of exacerbation;
2. p_2 – significant difference between the indices observed in patients from the main study group in the phase of exacerbation and the group of AHI with excessive body weight.

The obtained findings of the peripheral blood serum analysis showed that the course of chronic obstructive pulmonary disease (III degree of bronchial obstruction) in overweight patients in the phase of exacerbation is accompanied by more pronounced manifestations of systemic inflammatory process in the body, which shows up by the increased levels of TNF-

α , CRP and leptin by 1.3 times, 1.7 times and 1.8 times ($p1 < 0.001$), respectively, as compared to the indices observed in patients in the phase of remission; and 2.3 times, 4.0 times and 4.4 times ($p2 < 0.001$), respectively, as compared to the indices observed in the group of AHI (table 2).

Table 2: The levels of CRP, TNF- α and leptin in the examined COPD patients (III degree of bronchial obstruction) with overweight in different phases of the pathological process, ($M \pm m$)

Indices	AHI with excessive body weight, n = 12	Main study group n = 45		p_1	p_2
		Subgroup1, Remission phase, n = 18	Subgroup2, Exacerbation phase, n = 27		
TNF- α , pg/ml	113.20 \pm 13.60	207.74 \pm 2.34	265.79 \pm 4.95	<0.001	<0.001
CRP, mg/l	5.10 \pm 1.30	12.35 \pm 0.40	20.55 \pm 0.22	<0.001	<0.001
Leptin, ng/ml	12.00 \pm 2.40	29.50 \pm 4.10	53.10 \pm 4.70	<0.001	<0.001

Notes:

1. p_1 – significant difference between the indices observed in patients from the main study group in the phase of remission and the phase of exacerbation;
2. p_2 – significant difference between the indices observed in patients from the main study group in the phase of exacerbation and the group of AHI with excessive body weight.

Further investigations of the problem showed positive dynamics of the studied indicators after the course of comprehensive therapy. Particularly, on the 10th day, the concentration of CRP levels

in such patients decreased by 1.2 times ($p1 > 0.05$), and the level of TNF- α – by 1.4 times ($p1 < 0.05$), which made up (17.16 \pm 1.4) mg/l vs. (20.6 \pm 1.9) mg/l and (89.85 \pm 20.1) pg/ml vs. (265.8 \pm 22.3) pg/ml before treatment (table 3).

Table 3: The levels of CRP, TNF- α on the 10th day of treatment of the exacerbation phase of chronic obstructive pulmonary disease (III degree of bronchial obstruction) in overweight patients, (M \pm m)

Indices in subgroups of examined patients	AHI with excessive body weight, n = 12	COPD (III degree of bronchial obstruction) in overweight patients, n = 27		p ₁	p ₂	p ₃
		Before treatment	After treatment			
TNF- α , pg/ml	113.20 \pm 13.60	265.80 \pm 22.30	189.85 \pm 20.10	<0.05	<0.001	<0.01
CRP, mg/l	5.10 \pm 1.30	20.60 \pm 1.90	17.16 \pm 1.40	>0.05	<0.001	<0.001

Notes:

1. p₁ – significant difference of indices observed on the 10th day of treatment;
2. p₂ – significant difference of indices between the results observed in patients before the treatment and AHI;
3. p₃ – significant difference of indices between the results observed in patients after the treatment and AHI.

Positive dynamics observed in leptin indices was also the result of treatment adjustments. Thus, on the 10th day of treatment, its level decreased by 1.3 times ($p < 0.05$), as

compared to its indices before treatment, which made up (40.84 \pm 3.1) ng/ml vs. (53.1 \pm 4.7) ng/ml (table 4).

Table 4: The level of leptin on the 10th day of treatment of the exacerbation phase of chronic obstructive pulmonary disease (III degree of bronchial obstruction) in patients with overweight, (M \pm m)

Indices in subgroups of examined patients	AHI with excessive body weight, n = 12	COPD (III degree of bronchial obstruction) in overweight patients, n = 27		p ₁
		Before treatment	After treatment	
Leptin, ng/ml	12.00 \pm 2.40	53.10 \pm 4.70	40.84 \pm 3.10	<0.05

Note:

- p₁ – significant difference of indices observed at the beginning and on the 10th day of treatment. Three months after the treatment

Assessing the indices of systemic inflammation three months after the treatment, which involved the use of comprehensive treatment approach to the given pathology, we have observed a positive dynamics in the studied indices in patients of both subgroups, though these changes were more significant in patients of subgroup II, who agreed to modify their lifestyle.

Indices observed in patients of this subgroup showed a decrease in CRP concentration by 1.6 times and TNF- α level by 1.9 times ($p < 0.001$), which was (12.87 \pm 2.8) mg/l vs. 1.9 mg/l and (139.89 \pm 30.25) pg/ml vs. (265.8 \pm 22.3) pg/ml

before treatment. Positive changes, though not that significant, were observed in patients of group I. We have observed the decrease in CRP concentration by 1.4 times and TNF- α level by 1.6 times ($p < 0.05$), which was 14.75 \pm 2.1) mg/l vs. (20.6 \pm 1.9) mg/l and (166.25 \pm 31.21) pg/ml vs. (265.8 \pm 22.3) pg/ml before treatment. Leptin levels remained almost identical to those registered before treatment. Thus, three months after the beginning of treatment, the level of leptin decreased by only 1.1 times, which was (48.27 \pm 3.64) pg/ml vs. (53.1 \pm 4.7) pg/ml (table 5).

Table 5: Indices of systemic inflammation three months after the beginning of comprehensive therapy of chronic obstructive pulmonary disease (III degree of bronchial obstruction) in overweight patients, (M \pm m)

Indices, units of measurement	Subgroup I, n = 15		Subgroup II, n = 12		p ₁	p ₂
	Before treatment	After treatment	Before treatment	After treatment		
TNF- α , pg/ml	265.80 \pm 22.30	166.25 \pm 31.21	265.80 \pm 22.30	139.89 \pm 30.25	<0.05	<0.001
CRP, mg/l	20.60 \pm 1.90	14.75 \pm 2.1	20.60 \pm 1.90	12.87 \pm 2.80	<0.05	<0.001
Leptin, ng/ml	53.10 \pm 4.70	48.27 \pm 3.64	53.10 \pm 4.70	35.40 \pm 5.82	<0.05	<0.001

Notes:

1. p₁ – significant difference of indices observed in subgroup I at the beginning and three months after the treatment;
2. p₂ – significant difference of indices observed in subgroup II at the beginning and three months after the treatment.

The correlation analysis was used to study the impact of overweight on RF and inflammatory response in different phases of the pathological process.

We have noticed that in the remission phase the CRP level had a direct and strong correlation with TNF (rx, y = 0.82 \pm 0.20, $P < 0.001$), inverse and strong correlation with FEV1 (rx, y = -0.82 \pm 0.20, $P < 0.001$), inverse and moderate correlation with FVC (rx, y = -0.67 \pm 0.26, $P < 0.001$) and FEV/FVC (rx, y = -0.70 \pm 0.25 ($P < 0.001$)). The TNF level had an inverse and strong correlation with FEV1 (rx, y = -0.72 \pm 0.24, $P < 0.001$) and FVC (rx, y = -0.72 \pm 0.24, $P < 0.001$) and inverse and moderate correlation with FEV/FVC (rx, y = -0.50 \pm 0.31, $P < 0.001$) indices. In the exacerbation phase, the CRP level had a direct and moderate correlation with TNF (rx, y = 0.59 \pm 0.29, $P < 0.001$), inverse and a strong correlation with FEV1 (rx, y = -0.73 \pm 0.24, $P < 0.001$) and FEV/FVC (rx, y = -0.74 \pm 0.24, $P < 0.001$), and inverse and moderate correlation with FVC (rx, y = -0, 62 \pm 0.28, $P < 0.001$) indices.

The TNF level had an inverse moderate correlation with

FEV1 (rx, y = -0.43 \pm 0.32, $P < 0.001$), FVC (rx, y = -0.39 \pm 0.33, $P < 0.001$) and with FEV/FVC (rx, y = -0.34 \pm 0.33, $P < 0.001$) indices.

Thus, overweight has a negative influence on the course of COPD (III degree of bronchial obstruction) due to impairment of the respiratory function and activation of the inflammatory response. And the use of comprehensive therapy with xanthine medication and lifestyle modifications, made during the course of treatment, show improvement of patients' clinical symptoms, promote positive dynamics in terms of respiratory function and have even more positive effect on inflammatory activity, manifested by a significant decrease in the levels of CRP, TNF- α , leptin and helped to improve patients' quality of life.

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