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Immune Corrective Role of Statin Therapy in Patients with Chronic Obstructive Pulmonary Disease and Metabolic Syndrome

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Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases are considered as the leading causes of death and mortality in developed countries, the clinical significance of which increases progressively as far as the aging of population. in recent decades was formed COPD in a combination with metabolic syndrome (MS), which is another global disease of civilization and progress, which was a blend of overweight or obesity with hypertension, lipid and carbohydrate metabolism and diabetes. To correct the main manifestations of dyslipidemia as a major component of MS has been successfully using the statins all over the world. The aim of current study was to determine the effect of atorvastatin on parameters of cellular and humoral immune system and the functional activity of immune cells in patients with COPD, combined with MS. The study involved 43 patients with stage I COPD and presence of the metabolic syndrome and 75 patients with stage II COPD and metabolic syndrome. All patients were evaluated by indicators of immune status, which included the tests of I and II levels as required by the Memorandum of WHO. We established the immune-corrective role of statins (atorvastatin) in the treatment of patients with COPD, combined with MS, which is the presence of anti-inflammatory action, reducing the symptoms of autoimmune disorders, reducing the relative content of activated lymphocyte subpopulations and elimination of imbalance of the immune complexes.

Keyword: Chronic Obstructive Pulmonary Disease, Metabolic Syndrome, Atorvastatin, Immunity

1. Introduction

Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases are considered as the leading causes of death and mortality in developed countries, the clinical significance of which increases progressively as far as the aging of population [1]. Thus, according to the WHO in 2005 in the world among all deaths 30% occupied by cardiovascular causes, 13% - cancer, 2% - diabetes and 7% - COPD. It is believed that over the next 10 years, COPD will take second place as a cause of death in the population [2]. One of the classic features of a patient, who suffers from COPD, always has been reduced body weight as a result of muscular dystrophy, which is caused by disorder of metabolism under the influence of systemic inflammation, hypoxia, and prolonged use of β2-agonists. However, in recent decades was formed COPD in a combination with metabolic syndrome (MS), which is another global disease of civilization and progress, which was a blend of overweight or obesity with hypertension, lipid and carbohydrate metabolism and diabetes. Overweight alongside smoking are the main risk factors for general morbidity and mortality all over the world. Thus both overweight and smoking may interact synergistically and be associated with the development of insulin resistance, oxidative stress, and increased content of cytokines and

other inflammatory markers, which currently leads to endothelial dysfunction, cardiovascular disease and high risk of other diseases [3, 4]. In recent years, we can see active developing of the study of systemic effects in COPD when patients with this disease showing signs of diseases of the cardiovascular system and features of metabolic syndrome [5,6].

To correct the main manifestations of dyslipidemia as a major component of MS has been successfully using the statins all over the world. The appearance reductase inhibitors of 3-hydroxy-3-metylhlyutaryl-coenzyme A (HMG-CoA), or statins, have made a revolution in the treatment of hypercholesterolemia. Statins are drugs that are most commonly prescribed to treat these conditions because of their effectiveness in reducing the content of low density lipoprotein (LDL) and good tolerance and safety of use. It is known that chronic inflammatory changes in the immune system combined with changes in lipid metabolism in blood, liver, adipose and other tissues. In the scientific literature it is discussed two main mechanisms of integrating lipid metabolism and immune responses, one of which is associated with the synthesis of cholesterol and other - with activity of superfamily of nuclear X-receptors. It is proved that statins have a multi-pronged effect - anti-inflammatory, immunomodulatory and antiatherogenic.

Purpose of work – to determine the effect of atorvastatin on parameters of cellular and humoral immune system and the functional activity of immune cells in patients with COPD, combined with MS.

2. Materials and Methods

The study involved 43 patients with stage I COPD and presence of the metabolic syndrome (group 1) and 75 patients with stage II COPD and metabolic syndrome (group 2), the average age was 51.3 +4.2 years. The diagnosis of COPD is established according to the Order of Ministry of Health of Ukraine № 128 [7]. The diagnosis of MS was established on the basis of detailed anamnesis, clinical, laboratory and instrumental methods in identifying the main criteria for the syndrome on the recommendations of the International diabetes Federation (IDF), 2005 [8]. All patients were examined during remission of COPD and were treated with basic therapy of prolonged inhaled anticholinergic drugs and short on-demand drugs without inhaled corticosteroids. To correct the existing violations of lipid metabolism in MS, patients were treated with atorvastatin at a daily dose of 10 mg. To achieve the target blood pressure levels, all patients received enalapril at a daily dose of 20 - 40 mg, if not successful it was added amlodipine in dose of 10 mg. The control group consisted of 35 healthy persons randomized by age and sex, with no signs of MS and COPD. All patients were evaluated by indicators of immune status, which included the tests of I and II levels as required by the Memorandum of WHO [9]: quantitative assessment of the major populations and subpopulations of lymphocytes, determination of activated subpopulations of lymphocytes CD54 +, CD95 +, HLA-DR +, CD25 +, levels of pro-and anti-inflammatory cytokines determine spontaneous and mitogen-induced lymphocyte proliferative activity, the level of circulating immune complexes (CIC) of different molecular weight in the serum and the phagocytic activity of peripheral blood neutrophils, the concentration of serum immunoglobulins (IgG, IgA, IgM). Immunological examination was performed twice before carrying statin therapy and in the dynamics after 3 months of continuous use.

3. Results and Discussion

As a result of studies, we found that in the first group of patients with COPD I stage combined with MS, the main indicators of lymphocyte populations did not have probable differences in the values of the control group ($p > 0,1$) and did not significantly change in the dynamics of treatment (Table 1). The relative number of T, B lymphocytes and NK-cells had no significant differences in the values of the healthy people. The same trend was found for the percentage of key immunoregulatory subpopulations - T-helper and T-cytotoxic lymphocytes / suppressor whose content in the peripheral blood of patients in group 1 parameters consistent treatment of the dynamics of the control group ($p > 0,1$).

Table 1: The content of basic and activated populations and subpopulations of Lymphocytes in the peripheral blood of patients with COPD with MS in dynamic of treatment (M + m)

Indicator	Group 1 (n = 43)		Group II (n=75)		Control group (n=35)
	Before treatment	After treatment	Before treatment	After treatment	
Leukocytes, 10^9/л	6,24 ± 1,13	6,11± 1,18	6,36 ± 1,19	6,25 ± 1,09	6,76 ± 0,82
Lymphocytes, %	33,26 ± 1,31	32,85 ± 1,27	41,15 ± 2,75 *	36,42 ± 2,18* x	31,64 ± 3,90
$CD3^+$ lymphocytes, %	64,73 ± 3,45	65,28 ± 3,21	61,30 ± 2,86	64,55 ± 3,68	65,85 ± 6,55
$CD4^+$ lymphocytes, %	35,40 ± 1,84	34,74 ± 1,65	41,78 ± 1,86*	37,62 ± 1,26* x	33,23 ± 3,90
$CD8^+$ lymphocytes, %	22,48 ± 0,96	22,13 ± 1,04	17,24 ± 0,85*	18,28 ± 0,95 * *	21,50 ± 2,01
$CD4^+/CD8^+$	1,57 ± 0,11	1,56 ± 0,10	2,42 ± 0,13*	2,07 ± 0,11* x	1,55 ± 0,29
$CD22^+$ lymphocytes,%	25,54 ± 1,17	24,93 ± 1,15	31,45 ± 1,13*	27,56 ± 1,12 x	24,03 ± 1,50
$CD16^+$ lymphocytes,%	16,29 ± 0,87	17,03 ± 1,01	16,92 ± 0,93	17,34 ± 1,02	18,85 ± 2,30
$CD25^+$ lymphocytes,%	12,31±0,24*	9,03 ± 0,56 x	15,61±0,45*	11,74 ± 0,36* x	8,96±0,39
HLA-DR^+ lymphocytes,%	14,72 ± 0,31*	12,81 ± 0,32 x	17,61 ± 0,29*	15,47 ± 0,21* x	12,3±1,27
$CD95^+$ lymphocytes,%	4,98 ± 0,12*	3,14 ± 0,09 x	7,35 ± 0,11*	5,16 ± 0,08* x	3,04±0,09
$CD54^+$ lymphocytes,%	18,36 ±0,61*	14,28 ±0,37*x	21,02±1,01*	17,73 ± 0,89* x	11,07±1,65

Notes: - probability of difference of about the control ($p < 0.05$);
x- Probability of difference in dynamic of treatment ($p < 0.05$);
n- Number of patients

In the patients of the second group relative content of CD3 + and CD16 + cells in peripheral blood was not significant differences in the values in healthy ones as well as the dynamics of treatment, but it was discovered phenomenon of B-lymphocytosis, when the relative number of CD22 + cells exceeded the rate of the control group at 23, 59% ($p < 0,05$). In the dynamics of statin treatment was observed decrease in the percentage of CD22 + cells at 12,37% ($p < 0,05$), but with a significant predominance over the number of healthy patients to 12,81% ($p < 0,05$). In patients of the second group was found fundamental imbalance of immunoregulatory subopulyatsiy relative predominance of CD4 + T cells, leading to growth rate immunoregulatory index to 35.95% compared with healthy individuals. Such disturbances in the immune status are inherent, usually in patients with asthma when the basis for the pathogenesis of allergic inflammation is a reverse airflow obstruction, combined with the excessive formation of IgE. In our group of patients during the dilated bronchial test repeatedly confirmed irreversible airflow obstruction with no or little increase forced expiratory volume in 1 second, which is one of the main criteria for the diagnosis of COPD. Thus, these changes in the immune system that are in imbalance contents of T-helper cells and T-lymphocyte cytotoxic / suppressor due to the presence of MS, for which are typical autoimmune changes. In the dynamics of inclusion atorvastatin treatment was a significant decrease in immune regulatory index of 1.17

times, but it remained higher than the standard values at 25, 12% (p <0,05).
The content of activated lymphocyte subpopulations of CD25 + phenotype in patients of group 1 before treatment exceeded the control group on the rate of 37, 4% (p <0,05), but in the dynamics of treatment with atorvastatin inclusion it decreased by 26,6% (p <0,05) to normative values. In group II of patients the percentage of CD25 + lymphocytes exceeded the standard value at 74, 2% (p <0, 05), in the dynamics of treatment significantly decreased by 24, 8% (p <0, 05), but remained above the level of healthy individuals to 31, 03% (p <0,05). Similar changes were characteristic of activated HLA-DR + lymphocytes, the content of which in the first group of patients was higher than grandstanding healthy individuals at 16, 44% (p <0, 05), and the second - to 43, 17% (p <0.05) in the dynamic of treatment both parameters significantly decreased by 12.98% and 12.15%, but in the second group it remained significantly higher than in healthy individuals at 25, 77% (p <0, 05).
Number of activated lymphocytes that express FAS-receptor in patients of group 1 was significantly higher than the value of healthy individuals at 38,96% (p <0,05) and dynamic of treatment significantly decreased to normative values, while in the second group of patients was higher than normal - at 2.41 times (p <0,05), in dynamic of treatment decreased, but exceeded the rate in the control group in 1.70 times (p <0,05). The relative number of CD54 + subpopulation of lymphocytes in both groups of patients to treatment exceeded the rate of healthy persons in 1, 66 (p <0,05) and 1.90 times (p <0,05), in dynamic of treatment decreased the quantity of this subpopulation of lymphocytes however, their number exceeded the the level of healthy individuals at 29,01% (p <0,05) and 60,16% (p <0,05).

As it can be seen from the data presented in Table 2, spontaneous proliferative activity of lymphocytes in both groups of patients was increased without significant differences between them. In the dynamics of treatment was probable decline of index of spontaneous RBTL in group 1 (p <0,05) at 1.49 times the values of healthy individuals (p> 0,1), while in the second group - only 1.16 times (p <0,05), which exceeded the control group at 35,77% (p <0,05).
The index of stimulated PHA RBTL in group 1 had probable difference from healthy individuals in dynamic of treatment, and in patients of the second group during the primary examination, it was raised to 11,76% (p <0,05), and in dynamic of treatment significantly decreased to values of healthy individuals. Phagocytic activity of neutrophils, which was estimated by counting the number of phagocytes (NF) and phagocytic index (FI) in both groups of patients, was reduced.

Table 2: Dynamics of indicators of functional activity of immune competent cells in COPD patients with MS in dynamic of treatment (M + m)

Indicator	Group 1 (n = 43)		Group II (n=75)		Control group (n=35)
	Before treatment	After treatment	Before treatment	After treatment	
RBTL spontaneous%	2,87 ± 0,12 *	1,92±0,11* x	3,18±0,11*	2,74±0,09*x	1,76 ± 0,61
RBTL with PHA,%	80,24 ± 3,16	78,17±3,21	89,41±3,22*	79,45±3,06 x	80,0 ± 4,70
the number of phagocytes	5,02 ± 0,16*	5,61±0,18x	4,68±0,17*	5,31±0,21*x	6,50 ± 0,60
Phagocyte index,%	52,68±2,75*	63,24±2,84x	51,26±2,52*	60,21±2,43x	69,80 ± 7,20

Notes
* - probability of difference of index due to the control (p <0.05);
x - Probability of difference of index in dynamic of treatment (p <0.05);
n- Number of patients

The dynamics of treatment in group 1 figure SF increased by 11,75% (p <0,05), and FI - by 20,04% (p <0,05) to the values of the control group. In the second group also occurred Partly recovery parameters: phagocytic number increased to 13,46% (p <0,05), and the phagocytic index - by 17,46% (p <0,05), but did not reach the level of the control group.

Influence of statin therapy on serum concentrations of IgG and CIC is given in Table 3.

Table 3: Dynamics of indicators of humoral immune system in patients with COPD and MS (M + m)

Indicator	Group 1 (n = 43)		Group II (n=75)		Control group (n=35)
	Before treatment	After treatment	Before treatment	After treatment	
Ig G, g/l	14,75 ± 0,98	14,95±1,08	16,28±1,17*	16,36±1,05*	12,68±1,42
Ig A, g/l	1,31 ± 0,12	1,34±0,11	1,06 ±0,13*	1,02±0,18*	1,52±0,19
Ig M, g/l	0,96 ± 0,06	0,97±0,09	0,95±0,10	0,97±0,11	0,98±0,09
CIC large (> 19 S), conventional units	23,02 ± 0,41*	35,14±0,81 *x	21,17±0,49*	33,75±1,12* x	51,7±3,12
CIC medium (11-19S), conventional units	55,28 ± 2,36 *	42,73±1,22*x	61,55±2,34*	46,94±1,63 * x	34,54±2,02
CIC small (<11 S), conventional units	43,22 ± 1,64*	18,96±0,73*x	52,37±1,72*	24,39±1,05 * x	10,94±1,13

Notes
* - the probability of difference of the index in the control (p <0.05);
x - the probability of difference of the index in the dynamics of treatment (p <0.05);
n-number of patients

As can be seen from the data presented in Table 3 patients of group 1 in the dynamics of treatment with the inclusion of atorvastatin was seen likely changes in serum levels of IgG, IgM, IgA, their concentration is consistent with normative values (p> 0,1). In group II patients found an increased content of serum IgG and significantly lower than the control group level data IgA, the dynamics of treatment there was no significant change in both indicators, which may be due to the formation of antibodies in response to antigenic stimulation of microbial frequent exacerbations of COPD. In both groups, the patients with primary immunological study revealed an imbalance of serum CIC with a significant prevalence of pathogenic CIC content. Atorvastatin had a significant positive impact on content as pathogenic and physiological CIC. In group 1 content of the average molecular CIC significantly decreased by 29,37% (p <0,05), and small - to 127,95% (p <0,05), while increasing the content CIC large - at 52.65% (p <0,05). In group II patients the level of pathogenic CIC small and medium size was significantly higher than those of the healthy subjects and those of the group 1, the dynamics of inclusion atorvastatin treatment decreased their level respectively 1,31 (p <0,05) and 2.15 times (p <0,05), but both values significantly higher than levels in healthy individuals in 1,36 (p <0,05) and 2.23 times (p <0,05). The level of physiological CIC large size was reduced, and the dynamics of treatment increased to 1.59 times (p <0,05), but has not reached the performance of the control group and remained lower at 1.53 times (p <0,05).

Serum levels of cytokines in patients with COPD and MS in dynamics of treatment are presented in Table 4.

Table 4: Serum levels of cytokines in patients with COPD, combined with MS, in the dynamics of complex treatment (M ± m)

Indicator	Group 1 (n = 43)		Group II (n=75)		Control group (n=35)
	Before treatment	After treatment	Before treatment	After treatment	
ФНП-α, пг/мл	123,6 ±9,5*	61,5±5,7*x	126,9±7,5*	77,9±3,12*x	42,3±4,9
ІЛ-1β, пг/мл	110,6±7,1*	54,7±6,8 x	105,1±6,8*	72,6±3,82 * x	39,42±4,5
ІЛ-6, пг/мл	36,2±1,6*	17,8±1,9*x	68,3±2,2*	24,7±1,31 * x	10,31±2,3
ІЛ-4, пг/мл	22,4±1,7	24,7±1,8	17,5±1,1*	22,7±1,2 x	25,42±3,3

Notes

* - the probability difference of index in the control ($p < 0.05$);

x - The probability difference of index in the dynamics of treatment ($p < 0.05$);

n- Number of patients

As can be seen from the data presented in Table 4 patients of group 1 in serum was found increased proinflammatory cytokines TNF-α at 2.92 times ($p < 0,05$), IL-1β - at 2.81 times ($p < 0,05$) and IL - 6 - to 3.51 times ($p < 0,05$) compared with healthy individuals. The dynamics of the combined treatment was significant reduction in serum levels of proinflammatory cytokines, which, however, still higher than standard rates. In the second group of patients was also found growing content of proinflammatory cytokines, but the degree of increase was uneven with a significant prevalence of elevated levels of IL-6 (6.62 times relative standard values). The dynamics of treatment decreased serum concentrations of TNF-α at 1.64 times ($p < 0,05$), IL-1β - at 1.46 times ($p < 0,05$) and IL-6 - at 2.77 times ($p < 0,05$). However, their level is significantly lower than in healthy individuals. In the second group of patients with primary immunological study found reduced levels of anti-inflammatory IL-4, which after treatment was significantly increased to 1.3 times the level of healthy subjects ($p > 0,1$).

4. Conclusions.

1. Established immune-corrective role of statins (atorvastatin) in the treatment of patients with COPD, combined with MS, which is the presence of anti-inflammatory action, reducing the symptoms of autoimmune disorders, reducing the relative content of activated lymphocyte subpopulations and elimination of imbalance of the CIC.
2. In patients with stage II COPD, combined with MS appear to be more profound changes in the immune system, which is a partial recovery after a 3-month course of therapy with atorvastatin.
3. Revealed changes in the immune system and their partial recovery under the action of atorvastatin is the basis for the use of immune modulators in these patients.

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