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ABSTRACT

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EFFECTIVENESS OF COMPLEX TREATMENT OF PATIENTS WITH EARLY-ONSET AND LATE-ONSET BRONCHIAL ASTHMA ASSOCIATED WITH OBESITY

The **objective of the study** was a comparative assessment of the clinical effectiveness of atorvastatin and vitamin D effect on proteolytic activity in obese patients with BA depending on the age of BA onset.

Materials and Methods. We examined 195 patients with BA and obesity and 95 apparently healthy individuals. The patients were divided into 2 groups with regard to the age of BA onset: Group I included 100 patients with early-onset asthma, and Group II included 95 patients with late-onset asthma. Patients with complete BA control at baseline and those having achieved BA control after background therapy adjustment were excluded from further study. Patients of Groups I (n = 65) and II (n = 68) were divided into subgroups A, B, and C: patients of IA (n = 23) and IIA (n = 22) subgroups received background treatment in combination with vitamin D; patients of IB (n = 20) and IIB (n = 25) subgroups – in addition to background treatment received atorvastatin; patients of IC (n = 22) and IIC (n = 21) subgroups received only background treatment. To measure TIMP-1, MMP-1, and MMP-9 levels, IBL International GMBH enzyme-linked immunosorbent assay kits (Hamburg, Germany) were used. Asthma control was assessed using ACQ-5 (Asthma Control Questionnaire-5). The study was approved by the Bioethics Committee of the Academic and Research Medical Institute of Sumy State University. The obtained results were statistically processed using the SPSS–17 program.

The results of the study showed that MMP-1, MMP-9, and TIMP-1 levels in obese patients with late-onset BA were significantly higher vs. patients with early-onset BA. Background therapy and its combination with vitamin D or with atorvastatin contributed to a statistically significant decrease in the level of MMP-1, MMP-9, and

TIMP-1 in patients of IA, IB, and IC subgroups. MMP-1 level decreased significantly in patients with late-onset BA in all subgroups, but it was significantly lower in patients of IIB subgroup vs. IIA subgroup (p = 0.001) and IIC subgroup (p = 0.001). MMP-9 level decreased significantly in patients of IIA and IIB subgroups, but it was significantly lower in patients of IIB subgroup vs. IIA subgroup (p = 0.001) and IIC subgroup (p = 0.001). This suggested that atorvastatin contributed to a more significant decrease in MMP-9 level vs. background therapy and background therapy + vitamin D. TIMP-1 level decreased significantly only in patients of IIB subgroup and was lower vs. IIA subgroup (p = 0.001) and IIC subgroup (p = 0.001).

We demonstrated higher clinical treatment efficiency in patients of the IA subgroup who received vitamin D in addition to background therapy, which was confirmed by an increase in the level of BA control compared to that in patients of the B (p = 0.01) and C (p = 0.037) subgroups. In patients with late-onset BA (IIB subgroup), atorvastatin contributed to a better BA control compared to patients of IIA and IIC subgroups. The maximum improvement of respiratory function in patients with early-onset BA was achieved with the combination of background therapy + vitamin D, while in patients with late-onset BA – with atorvastatin.

Conclusions. The use of atorvastatin has a more significant impact on the level of remodeling markers, BA control, and respiratory function in obese patients with late-onset BA vs. early-onset BA. Better BA control and maximum improvement of respiratory function in obese patients with early-onset BA were achieved with the combination of background therapy + vitamin D.

Keywords: bronchial asthma, obesity, onset, matrix metalloproteinase-1, -9, tissue inhibitor of matrix metalloproteinase-1, control, respiratory function, atorvastatin, vitamin D.

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ЕФЕКТИВНІСТЬ КОМПЛЕКСНОГО ЛІКУВАННЯ ХВОРИХ НА БРОНХІАЛЬНУ АСТМУ, АСОЦІЙОВАНУ ІЗ ОЖИРІННЯМ, ІЗ РАННІМ І ПІЗНІМ ДЕБЮТОМ

Мета дослідження: порівняльна оцінка клінічної ефективності впливу на металопротеолітичну активність базисної терапії із аторвастатином та вітаміном D хворих на БА із ожирінням залежно від віку дебюту.

Матеріал і методи дослідження. Обстежено 195 хворих на БА із ожирінням і 95 практично здорових осіб. Пацієнтів розподілено на дві групи залежно від віку дебюту БА: 100 хворих із раннім дебютом склали I групу, 95 із пізнім – II групу. Пацієнти із повним контролем на початковому етапі та ті, які досягли контролю після корекції базисного лікування, були виключені з подальшого дослідження. Пацієнти I (n = 65) та II груп (n = 68) були поділені на підгрупи А, Б і В: ІА (n = 23) та ІІА (n = 22) підгрупи отримували базисне лікування у поєднанні з вітаміном D; ІБ (n = 20) та ІІБ (n = 25) – з аторвастатином; ІВ (n = 22) та ІІВ

(n = 21) – лише базисне. Визначення ТІМП-1, ММП-1 і ММП-9 здійснювали за допомогою наборів для імуноферментного аналізу IBLInternationalGMBH (Hamburg, Germany). Оцінку контролю БА здійснювали за допомогою опитувальника ACQ-5. Дослідження було схвалено Комісією з питань біоетики навчально-наукового медичного інституту Сумського державного університету. Статистичний аналіз отриманих результатів проводили за допомогою SPSS-17 програми.

Результати дослідження показали, що вміст ММП-1, -9 та ТІМП-1 у хворих на пізню БА із ожирінням вірогідно вищий порівняно із ранньою. Базисна терапія та її поєднання із вітаміном D і з аторвастатином сприяли вірогідному зниженню вмісту ММП-1, ММП-9, ТІМП-1 у хворих ІА, ІБ, ІВ підгруп. Вміст ММП-1 вірогідно знижувався у хворих на пізню БА всіх підгруп, але у ІІБ підгрупі був нижчим порівняно із таким у хворих ІІА (p = 0,001) та ІІВ (p = 0,001) підгруп. Вміст ММП-9 вірогідно знижувався у хворих ІІА та ІІБ підгруп, але у хворих ІІБ підгрупи був нижчим порівняно із таким у ІІБ (p = 0,001) та у ІІВ (p = 0,001) підгрупах. Це свідчить про те, що залучення аторвастатину сприяло більш вагомому зниженню ММП-9 порівняно з базисною терапією та її поєднанням з вітаміном D. Вміст ТІМП-1 вірогідно знижувався лише у хворих ІІБ підгрупи та був нижчим порівняно з таким у ІІА (p = 0,001) та ІІВ (p = 0,001) підгрупах.

Встановлено вищу клінічну ефективність лікування у хворих ІА підгрупи, які отримували у доповнення до базисної терапії вітамін D, що підтверджено підвищенням рівня контролю порівняно із таким у хворих Б (p = 0,01) та В (p = 0,037) підгруп. У хворих ІІБ підгрупи залучення аторвастатину сприяло вищому контролю порівняно із хворими ІІА та ІІВ підгруп. ФЗД максимально зростала у хворих на ранню БА при залученні до базисного лікування вітаміну D, а у хворих на пізню – при залученні аторвастатину.

Висновки. Застосування аторвастатину більш вагомо впливає на вміст маркерів ремоделювання, рівень контролю, ФЗД у хворих на пізню БА із ожирінням порівняно із ранньою. у хворих на пізню БА із ожирінням. Вищий контроль та максимальне покращення ФЗД у хворих на ранню БА із ожирінням були досягнуті за допомогою поєднання базисної терапії з вітаміном D.

Ключові слова: бронхіальна астма, ожиріння, дебют, матриксні металопротеїнази-1, -9, тканинний інгібітор матриксних металопротеїназ-1, контроль, функція зовнішнього дихання, аторвастатин, вітамін D.

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INTRODUCTION / ВСТУП

Current recommendations for the treatment of bronchial asthma (BA) are aimed at controlling symptoms, minimizing the risk of exacerbations and airflow restriction, and inhibiting airway remodeling, but their effectiveness is poor in patients with BA and obesity. Therefore, using remodeling markers as a treatment target is an urgent problem in

BA therapy, since there are no specific medications aimed at inhibiting their activity [1, 2, 3, 4].

The lower probability of achieving control and shorter control duration in obese asthma patients compared to patients with healthy weight [5, 6] is partially explained by the higher activity of the inflammatory process [7], its neutrophilic type [5, 8], as well as higher indicators of remodeling markers [9]. A number of studies have shown that glucocorticoids (GCs) affect both airway inflammation and remodeling processes in BA, although their effect on the extracellular matrix and the content of matrix proteinases (MMPs), tissue inhibitor of matrix metalloproteinases (TIMP)-1 is not very pronounced [10, 4]. In light of this and due to the lack of targeted special pharmacotherapy of the BA-obesity phenotype [5, 6], as well as the lack of pharmacological methods of inhibiting airway remodeling [3], we consider it reasonable to search for pathogenetically substantiated medications which could complement the limited effect of background therapy on remodeling processes and ensure higher effectiveness of treatment. As such medications, we considered statins, which are able to inhibit inflammation, production of MMP [11, 12, 13], IL-17 [14] and fibronectin, and fibroblast differentiation in response to TGF-β_1 [15]. Along with statins, we focused on the use of vitamin D. Our choice was based on the fact that vitamin D deficiency is often observed in obese people. Moreover, this vitamin can suppress the expression of TGF-β_1 and ECM markers, and inhibit pulmonary fibrosis [16, 17, 18]. These days, the phenotypic features have been actively studied in terms of etiology, pathogenesis, clinical manifestations, and effectiveness of treatment in obese patients with BA depending on the age of onset [19]. Therefore, the **objective of the study** was a comparative assessment of the clinical and laboratory effectiveness of atorvastatin and vitamin D inclusion in the background therapy of obese patients with BA depending on the age of onset.

Materials and Methods. 195 BA patients with obesity were examined. The control group consisted of 95 apparently healthy individuals with no history of allergy and atopy symptoms. All of the patients had previously signed an informed consent form. The patients were divided into two clinical groups according to the BA onset: Group I included 100 patients with early-onset asthma, and Group II included 95 patients with late-onset asthma. 12 (12.0%) patients with early onset and 5 (5.3%) patients with late onset achieved complete BA control and were excluded from the study. All patients had their inhaled GCs doses adjusted; they underwent assessment of BA control in 4 weeks, after which 65 patients with early-onset BA and 68 patients with late-onset BA, who had partial or poor control, continued participation in the study. In order to study the influence of atorvastatin and vitamin D on remodeling markers level and clinical efficacy, patients of Group I (n = 65) and Group II (n = 68) were randomized into three subgroups A, B, and C depending on the prescribed treatment. Patients of IA (n = 23) and IIA (n = 22) subgroups received background treatment in combination with vitamin D at a dose of 4000 IU; patients of IB (n = 20) and IIB (n = 25) subgroups – in addition to background treatment received atorvastatin 10 mg per day; patients of IC (n = 22) and IIC (n = 21) subgroups received only background treatment. BA diagnosis and BA severity were determined according to the GINA Recommendations 2016 and its later versions. Obesity was diagnosed in accordance with the Order of the Ministry of Health of Ukraine № 574 dated 05.08.2009 "On approval of the protocols for medical care for patients with endocrine diseases" and the WHO recommendations (1999), the European Association for the Study of Obesity (EASO, 2016). To measure TIMP-1, MMP-1, and MMP-9 levels, IBL International GMBH enzyme-linked immunosorbent assay kits (Hamburg, Germany) were used. Asthma control was assessed using ACQ-5 (Asthma Control Questionnaire-5). The study was approved by the Bioethics Committee of the Academic and Research Medical Institute of Sumy State University. The obtained results were statistically processed using the SPSS–17 program.

Results. Taking into account the heterogeneity of the pathogenetic mechanisms of remodeling in different BA phenotypes [20, 3], we investigated the content of remodeling markers in obese patients with BA depending on the age of BA onset. The results of the study of MMP-1, MMP-9, and TIMP-1 levels in blood serum in obese patients with early-onset BA and the effect of our proposed treatment on their content are presented in Table 1.

Before treatment modification, MMP-1, MMP-9, and TIMP-1 indicators did not differ significantly (all p's > 0.05) among subgroups A, B, and C in patients of Group I and were significantly higher (46.8 ± 1.77; 43.4 ± 1.39, and 43.3 ± 1.13 ng/ml, respectively) vs. the control group. Background therapy (subgroup C), its combination with vitamin D (subgroup A) and with atorvastatin (subgroup B) contributed to a statistically significant decrease in the level of MMP-1, MMP-9, and TIMP-1, but had no effect on the MMP-9/TIMP-1 ratio.

Table 1 – Longitudinal treatment data on the level of matrix metalloproteinases and tissue inhibitor of matrix metalloproteinases-1 in patients with early-onset bronchial asthma and obesity

Group	MMP-1	p	p^1	MMP-9	p	p^1
IA, n = 23	1150.39 (32.0–335.0)	$^{a-b}$ 0.527	0.001	204.6 (96.0–365.0)	$^{a-b}$ 0.534	
	1134.91 (23.0–258.0)	$^{a-b}$ 0.817		195.8 (95.0–376.0)	$^{a-b}$ 0.145	0.001
IB, n = 20	1173.15 (33.0–345.0)	$^{b-c}$ 0.087	0.001	181.90 (25.0–345.0)	$^{b-c}$ 0.687	
	1137.85 (30.0–320.0)	$^{b-c}$ 0.091		166.9 (20.0–330.0)	$^{b-c}$ 0.950	0.001
IC, n = 22	1134.14 (32.0–330.0)	$^{a-c}$ 0.414	0.005	187.4 (56.0–378.0)	$^{a-c}$ 0.318	
	990.05 (33.0–210.0)	$^{a-c}$ 0.035		163.5 (60.0–305.0)	$^{a-c}$ 0.284	0.005
	TIMP-1	**p**	**p^1**	**MMP-9/TIMP-1**	**p**	**p^1**
IA, n = 23	146.7 (25.0–312.0)	$^{a-b}$ 0.083		2.16 (0.46–7.77)	$^{a-b}$ 0.028	
	135.8 (35.0–307.0)	$^{a-b}$ 0.082	0.001	2.13 (0.49–8.35)	$^{a-b}$ 0.017	0.089
IB, n = 20	122.3 (25.0–633.0)	$^{b-c}$ 0.326		3.71 (0.51–7.92)	$^{b-c}$ 0.023	
	108.3 (23.0–509.0)	$^{b-c}$ 0.442	0.001	3.73 (0.63–8.48)	$^{b-c}$ 0.012	0.191
IC, n = 22	124.8 (25.0–302.0)	$^{a-c}$ 0.446		2.71 (0.52–9.58)	$^{a-c}$ 0.586	
	109.3 (30.0–299.0)	$^{a-c}$ 0.312	0.001	2.68 (0.61–10.17)	$^{a-c}$ 0.699	0.709

Notes:

1. Numerator - before treatment;
2. Denominator – after treatment;
3. p^{a-b} – statistically significant difference between the indicators in subgroups A and B;
4. p^{b-c} – statistically significant difference between the indicators in subgroups B and C;
5. p^{a-c} – statistically significant difference between the indicators in subgroups A and C;
6. p^1 – statistically significant difference between the indicators in patients of one group before treatment modification and after 12 weeks of treatment

The results of the study of MMP-1, MMP-9, and TIMP-1 levels in obese patients with late-onset BA depending on the treatment are shown in Table 2.

Baseline values of MMP-1, MMP-9, and TIMP-1 were significantly higher vs. the control group (46.8 ± 1.77; 43.4 ± 1.39, and 43.3 ± 1.13 ng/ml, respectively), did not differ significantly among subgroups (all p's > 0.05) and decreased significantly in all groups. MMP-1 level was significantly lower in patients of IIB subgroup vs. IIA subgroup (p = 0.001) and IIC subgroup (p = 0.001). In 12 weeks, MMP-9 level decreased significantly in patients of IIA and IIB subgroups vs. baseline values, but it was significantly lower in patients of IIB subgroup vs. IIA subgroup (p = 0.001) and IIC subgroup (p = 0.001); in IIC subgroup, MMP-9 level remained at the baseline level. This suggested that atorvastatin contributed to a more significant decrease in MMP-9 level vs. background therapy and background therapy + vitamin D. TIMP-1 level decreased significantly only in patients of IIB subgroup and was lower vs. IIA subgroup (p = 0.001) and IIC subgroup (p = 0.001). MMP-9/TIMP-1 ratio decreased significantly in patients of subgroups A, B, and C and depended on the method of treatment. This value

was significantly lower in patients of IIB subgroup vs. IIA subgroup (p = 0.002).

Before treatment modification, control indicators did not differ among subgroups A, B, and C in patients with early-onset BA, but after 12 weeks of treatment, patients of subgroup A achieved better control compared to patients of subgroup B (p = 0.001) and subgroup C (p = 0.001) (Table 3). Assessment of late BA control progression showed that BA control improved in all groups; however, patients of the IIB subgroup achieved significantly better BA control vs. the IIA subgroup (p = 0.001) and IIC subgroup (p = 0.001).

Table 2 – Longitudinal treatment data on the level of matrix metalloproteinases and tissue inhibitor of matrix metalloproteinases-1 in patients with late-onset bronchial asthma and obesity

Group	MMP-1	p	p^1	MMP-9	p	p^1
IIA, n = 22	222.0 (110.0–376.0)	$^{a-b}$ 0.502		208.1 (56.0–545.0)	$^{a-b}$ 0.932	
	218.6 (110.0–365.0)	$^{a-b}$ 0.001	0.026	196.8 (45.0–507.0)	$^{a-b}$ 0.001	0.001
IIB, n = 25	232.8 (33.0–345.0)	$^{b-c}$ 0.155		203.9 (101.0–356.0)	$^{b-c}$ 0.708	
	96.5 (45.0–165.0)	$^{b-c}$ 0.001	0.001	74.2 (34.0–230.0)	$^{b-c}$ 0.001	0.001
IIC, n = 21	197.2 (98.0–356.0)	$^{a-c}$ 0.325		213.9 (102.0–365.0)	$^{a-c}$ 0.697	
	181.1 (95.0–311.0)	$^{a-c}$ 0.152	0.005	211.8 (105.0–378.0)	$^{a-c}$ 0.473	0.876
	TIMP-1	**p**	**p^1**	**MMP-9/TIMP-1**	**p**	**p^1**
IIA, n = 23	213.6 (120.0–354.0)	$^{a-b}$ 0.856		1.54 (0.58–3.38)	$^{a-b}$ 0.966	
	210.3 (132.0–366.0)	$^{a-b}$ 0.001	0.394	1.19 (0.24–2.54)	$^{a-b}$ 0.002	0.026
IIB, n = 20	227.4 (103.0–598.0)	$^{b-c}$ 0.270		1.82 (0.7–5.44)	$^{b-c}$ 0.515	
	135.4 (65.0–345.0)	$^{b-c}$ 0.001	0.001	0.69 (0.12–2.25)	$^{b-c}$ 0.137	0.001
IIC, n = 22	239.0 (103.0–388.0)	$^{a-c}$ 0.135		1.43 (0.39–2.93)	$^{a-c}$ 0.610	
	228.3 (98.0–375.0)	$^{a-c}$ 0.375	0.052	0.78 (0.21–1.77)	$^{a-c}$ 0.031	0.023

Notes:

1. p^{a-b} – statistically significant difference between the indicators in subgroups A and B;
2. p^{b-c} – statistically significant difference between the indicators in subgroups B and C;
3. p^{a-c} – statistically significant difference between the indicators in subgroups A and C;

p^1 – statistically significant difference between the indicators in patients of one group before treatment modification and after 12 weeks of treatment

The results of respiratory function examination in patients of Groups I and II depending on the treatment method are shown in Table 4.

As we can see, in patients of Group I, FEV_1 significantly increased in subgroups A and B, while in subgroup C there was an increasing trend. Thus, in subgroup A, FEV_1 increased by 13.3%, in subgroup B – by 7.5%, and in subgroup C – only by 1.8% compared to the baseline level. FVC significantly increased only in subgroup A (p = 0.003). An increase in ΔFEV_1 was observed in all subgroups, but did not differ significantly. In patients of Group II, a significant increase of FEV_1 was observed in subgroups A, B, and C. At the same

time, FEV_1 was higher in patients of IIB subgroup vs. IIA subgroup (p = 0.001) and IIC subgroup (p = 0.031). FVC and FEV_1/VC increased significantly only in the IIA and IIB subgroups, while ΔFEV_1 demonstrated a slight increasing trend.

Table 3 – Longitudinal treatment data on the level of BA control in patients with bronchial asthma and obesity

Subgroup	Before treatment modification	p	After 12 weeks	p	P[1]
Early onset					
A, n = 23	2.74 (1.6–4.2)	[a-b] 0.510	0.68 (0.3–1.4)	[a-b] 0.001	0.001
B, n = 20	2.86 (2.0–3.8)	[b-c] 0.620	1.04 (0.4–1.4)	[b-c] 0.037	0.001
C, n = 22	2.97 (2.0–3.4)	[a-c] 0.231	1.19 (0.2–3.2)	[a-c] 0.001	0.551
Late onset					
A, n = 22	2.32 (1.5–4.2)	[a-b] 0.123	1.54 (0.45–3.0)	[a-b] 0.001	0.001
B, n = 25	2.54 (1.6–3.6)	[b-c] 0.135	0.83 (0.2–1.5)	[b-c] 0.001	0.001
C, n = 21	2.16 (1.6–3.2)	[a-c] 0.990	1.95 (1.0–2.7)	[a-c] 0.017	0.012

Discussion. Considering the inconsistent results of studies assessing the levels of MMP-1, MMP-9, and TIMP-1 in patients with BA and obesity [21, 22] and the heterogeneity of the pathogenetic mechanisms of remodeling in different BA phenotypes [20, 3], we differentially investigated the content of remodeling markers depending on the age of BA onset. We observed an increase in the content of MMP-1, -9, and TIMP-1 in obese patients with early-onset and late-onset BA compared to apparently healthy individuals. At the same time, the level of remodeling markers was significantly higher in late-onset BA compared to early-onset BA. The higher content of MMP-1 and MMP-9 in obese patients with late-onset BA can be partially explained by TIMP-1-mediated prolongation of neutrophil survival and activation of neutrophilic inflammation through the secretion of neutrophil elastase and myeloperoxidase [23]. It is obvious that the obtained data regarding the difference in remodeling marker levels observed in different obesity-associated BA phenotypes added to the results of researchers who claim the heterogeneity of the mechanisms of its occurrence and progression, which leads to specific endotypes of airway remodeling in BA [20, 3].

At the next stage, we investigated the effect of background therapy and its combination with atorvastatin and vitamin D on the content of remodeling markers. We found that the effect of background therapy on MMP-1, MMP-9, and TIMP-1 levels was less pronounced compared to combined therapy involving atorvastatin. A particularly effective impact on these markers was observed with atorvastatin in obese patients with late-onset BA: they had the highest level of remodeling markers. In these patients, we observed a 2.4-fold, 2.7-fold, and 1.7-fold decrease in MMP-1, MMP-9, and TIMP-1 levels, respectively, while treatment with background therapy and background therapy + vitamin D did not demonstrate such a trend. A less pronounced effect on the content of remodeling markers can be explained by the fact that iGCs have more impact on the activity of inflammation rather than on remodeling, while the presence of bronchial structural changes is responsible for the limited clinical response [2]. However, a number of studies have shown that GCs affect both airway inflammation and remodeling processes in BA, although their effect on extracellular matrix, MMP, and TIMP is not very pronounced [10]. The results obtained in the study are consistent with the data of Thomson NC (2015), who showed that treatment with atorvastatin alone or in combination with iGCs reduced the levels of pro-inflammatory cytokines, chemokines, and growth factors unresponsive to inhaled corticosteroids alone, as well as the levels of MMP-8 and MMP-9, compared to monotherapy with inhaled corticosteroids [24]. Statins also reduced the levels of inflammatory biomarkers – high-sensitivity C reactive protein, interleukin-6, interleukin-8, and sCD14 and the secretion of monocyte chemoattractant protein-1. It led to a decreased recruitment of leukocytes during inflammation, which was associated with a decrease in the content of remodeling markers as well as with a significant decrease in metabolic disorders and levels of pro-inflammatory cytokines [25, 26].

Table 4 – Longitudinal data on the respiratory function assessment in patients with bronchial asthma and obesity depending on treatment

Subgroup	Before treatment modification	p	After 12 weeks	p	p[1]
Early onset					
FEV_1					
A, n = 23	59.9 (43.0–72.0)	a-b 0.192	67.8 (55.0–78.0)	a-b 0.006	0.001
B, n = 20	56.9 (44.0–82.0)	b-c 0.782	61.2 (46.0–82.0)	b-c 0.413	0.001
C, n = 22	57.1 (41.0–76.0)	a-c 0.328	58.1 (44.0–75.0)	a-c 0.002	0.06
FVC					
A, n = 23	77.6 (43.0–72.0)	a-b 0.99	82.4 (68.0–99.0)	a-b 0.510	0.003
B, n = 20	77.2 (55.0–99.0)	b-c 0.820	79.1 (65.0–99.0)	b-c 0.479	0.063
C, n = 22	75.9 (36.0–99.0)	a-c 0.874	76.2 (43.0–99.0)	a-c 0.145	0.317
FEV1/VC					
A, n = 23	82.3 (49.0–108.0)	a-b 0.043	82.2 (69.0–96.0)	a-b 0.09	0.99
B, n = 20	74.3 (55.6–103.0)	b-c 0.743	77.5 (60.0–103.0)	b-c 0.830	0.008
C, n = 22	77.7 (47.5–108.0)	a-c 0.180	77.6 (49.0–115.0)	a-c 0.064	0.873
ΔFEV_1					
A, n = 23	13.2 (11.0–18.0)	a-b 0.04	14.3 (10.0–19.0)	a-b 0.193	0.002
B, n = 20	14.2 (12.0–18.0)	b-c 0.313	15.9 (11.0–25.0)	b-c 0.751	0.004
C, n = 22	13.6 (10.0–17.0)	a-c 0.351	15.1 (10.5–19.0)	a-c 0.312	0.001
Late onset					
FEV_1					
A, n = 22	54.8 (42.0–72.0)	a-b 0.054	59.7 (47.0–72.0)	a-b 0.001	0.001
B, n = 25	60.7 (56.0–78.0)	b-c 0.762	68.7 (56.0–78.0)	b-c 0.031	0.001
C, n = 21	57.7 (36.0–83.0)	a-c 0.474	59.9 (41.0–83.0)	a-c 0.900	0.05
FVC					
A, n = 22	73.3 (48.0–97.0)	a-b 0.058	76.4 (56.0–97.0)	a-b 0.006	0.003
B, n = 25	81.4 (65.0–98.0)	b-c 0.650	85.4 (72.0–98.0)	b-c 0.073	0.005
C, n = 21	78.5 (51.0–99.0)	a-c 0.296	80.6 (67.0–97.0)	a-c 0.203	0.167
FEV1/VC					
A, n = 22	76.2 (46.4–95.0)	a-b 0.865	78.8 (53.0–99.0)	a-b 0.257	0.033
B, n = 25	75.5 (52.4–93.6)	b-c 0.990	81.3 (68.0–92.0)	b-c 0.141	0.001
C, n = 21	74.3 (37.5–105.0)	a-c 0.683	74.9 (43.0–105.0)	a-c 0.496	0.873
ΔFEV_1					
A, n = 22	12.3 (8.0–18.0)	a-b 0.170	12.4 (7.0–19.0)	a-b 0.181	0.485
B, n = 25	13.6 (8.0–19.0)	b-c 0.676	14.2 (8.0–21.0)	b-c 0.692	0.07
C, n = 21	13.3 (8.0–20.0)	a-c 0.208	13.5 (8–21.0)	a-c 0.359	0.319

We obtained data on higher clinical efficiency in patients of the IA subgroup who received vitamin D in addition to background therapy, which was confirmed by an increase in the level of BA control compared to that in patients of the B ($p = 0.01$) and C ($p = 0.037$) subgroups. Thus, the combination of vitamin D and background therapy did not significantly affect MMP and TIMP-1 levels vs. background therapy alone. However, vitamin D is known to inhibit the airway remodeling process in obese asthmatic patients without affecting the levels of MMP and TIMP-1, to prevent the increase in the expression of TGF-β_1 and to have a synergistic effect with anti-asthmatic drugs [27, 18, 28].

In patients with late-onset BA (IIB subgroup), atorvastatin contributed to a better BA control compared to patients of IIA and IIC subgroups. It is consistent with the results of a meta-analysis by Thomson NC (2015), which demonstrated a statin-induced reduction in symptoms in asthmatic smokers, which was associated with some local anti-inflammatory effects in the airways and reduction in emergency room visits, oral GCs use, and hospitalizations. These patients were characterized by neutrophilic inflammation accompanied by increased proteolytic activity [24], which could be reduced by statins. According to Holguin (2011), patients with late-onset BA and obesity also have a neutrophilic type of inflammation [19]. The effect of statins on BA symptoms due to their anti-inflammatory effect was confirmed in a study by Nageeb ES (2019) [13]. The use of atorvastatin improved ACT scores compared to placebo [12]. Also, atorvastatin reduced the frequency of hospitalizations/emergency visits for asthma [29]. The obtained data confirm that statins contribute to the prevention of exacerbations and to control of BA symptoms and can be used as an additional therapy.

Airways remodeling may also explain the irreversibility of bronchial obstruction and resistance to treatment and should be a potential therapeutic target in patients with BA and obesity, who are characterized by more severe symptoms and worse prognosis [9].

Meta-analysis of Sunata K (2022) including 11 randomized controlled studies and 8 observational studies showed that statins improved ACT scores and ACQ scores compared to placebo and reduced asthma-related emergency room visits; however, statins did not improve pulmonary function [30]. Another meta-analysis confirmed the positive effect of statins in terms of clinical symptom reduction in patients with BA according to the ACQ and ACT scores; also, statins decreased C-reactive protein level in blood serum and the number of eosinophils in sputum with no improvement in pulmonary function [31]. Obese patients with severe asthma taking statins were found to have better control of asthma symptoms according to ACT score vs. non-statin users, but there was no statistically significant difference in pulmonary function, use of GCs or bronchodilators, and peripheral eosinophilia between the two groups [32, 33]. The results of this study also showed that patients with severe BA might benefit from the addition of statins to their treatment. Since the study population was comprised of obese subjects, the asthma-obese phenotype may be a target for further clinical trials evaluating the safety and efficacy of statins in severe asthma. Despite the lack of difference in spirometry and peak flow measurements in some studies, a better BA control according to ACQ score and reduced risk of exacerbations have been proved, which indicates a positive effect of statins in BA treatment [34, 11]. However, another study also proved the role of statins in improving respiratory function [35].

In our study, a statistically significant increase in FEV_1 was observed in patients of IA (13.3%) and IB (7.5%) subgroups, but it was significantly higher in the IA subgroup vs. IB ($p = 0.006$) and IC ($p = 0.002$) subgroups. FVC significantly increased only in subgroup A ($p = 0.003$). An increase in ΔFEV_1 was observed in all subgroups, but did not differ significantly.

In patients of Group II, a significant increase of FEV_1 was observed in subgroups A, B, and C. At the same time, FEV_1 was higher in patients of IIB subgroup vs. IIA subgroup ($p = 0.001$) and IIC subgroup ($p = 0.031$). FVC and FEV_1/VC increased significantly only in the IIA and IIB subgroups, while ΔFEV_1 demonstrated a slight increasing trend. The impact of atorvastatin on respiratory function in patients of the IIB subgroup was consistent with the results of Sun S. et al. (2017), who reported that statins reduced leptin levels and improved respiratory function in obese patients with BA [35].

Alabed M (2022) showed in his study that statins complemented the current background therapy of BA by means of providing effect on several mechanisms involved in the inflammation and remodeling processes and could be a potential therapeutic option for different BA phenotypes [36]. Our results optimized the use of statins by clarifying the possibility and feasibility of using statins in patients with BA: we demonstrated their significant effect on the remodeling marker levels and clinical

efficacy (BA control, respiratory function) specifically in obese patients with late-onset BA. Thus, we identified a subgroup of patients with statin-sensitive BA, i.e. obese patients with late-onset BA, for whom statins might be most useful.

CONCLUSIONS / ВИСНОВКИ

MMP-1, MMP-9, and TIMP-1 levels were significantly higher in obese patients with early-onset and late-onset BA vs. apparently healthy individuals and were significantly higher in obese patients with late-onset BA vs. obese patients with early-onset BA.

In early-onset BA, background therapy and its combination with vitamin D or with atorvastatin contributed to a statistically significant decrease in the level of MMP-1, MMP-9, and TIMP-1.

Administration of atorvastatin in obese patients with late-onset BA contributed to a more significant decrease in MMP-1, MMP-9, and TIMP-1 levels vs. background therapy or background therapy + vitamin D.

We demonstrated higher clinical treatment efficiency in patients of the IA subgroup who received vitamin D in addition to background therapy, which was confirmed by an increase in the level of BA control compared to that in patients of the B ($p = 0.01$) and C ($p = 0.037$) subgroups. In patients of the IIB subgroup, atorvastatin contributed to a better BA control compared to patients of the IIA subgroup (background therapy + vitamin D) and IIC subgroup (background therapy).

The maximum improvement of respiratory function in obese patients with early-onset BA was achieved with the combination of background therapy + vitamin D, and in obese patients with late-onset BA – with atorvastatin.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

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