REFERENCES

1. Lopatin AS, Petrov VI, Slizova TA, Ponomareva YuV. [Allergic rhinitis: pharmacoeconomic aspects]. Atmosfera. 2003;4:47-50. Russian.
2. Aleshina RM. [Specific immunotherapy is an effective method of basic treatment for atopic bronchial asthma]. ImunologIya ta alergologIya. 1998;1/2:115-9. Russian.
3. Bulgakova VA, Balabolkin II, Ksenzova LD. [Modern trends in pharmacotherapy of allergic rhinitis in children]. Voprosyi sovremnoy pediatrii. 2007;6:85-91. Russian.
4. Goryachkina LA. [Modern antihistamines in the treatment of allergic diseases]. RinologIya. 2002;1:70-76. Russian.
5. Guschin IS. [Pathophysiology of allergy]. Ros. rinologiya. 2004;1:6-22. Russian.
6. Drannik GN [Clinical Immunology and Allergology]. Kyiv, OOO «Poligraf plyus». 2010:1-552. Russian.
7. Emelyanov AV [Modern ideas about the diagnosis and treatment of allergic rhinitis]. Lechaschiy vrach. 2003;3:4-11. Russian.
8. Zaykov SV. [Are there approaches to the diagnosis and treatment of allergic rhinitis in Ukraine and the EU?]. Klinichna Imunologiya. Alergologiya. Infektologiya. 2007;2:13-16. Russian.
9. Zaykov SV. [Modern ideas about the treatment of pollinosis]. Klinich. Imunologiya. Alergologiya. Infektologiya. 2008;3(14):49-54. Russian.
10. [Clinical Alergology and Immunology: A Guide for Practitioners]. Goryachkinoy LA, Kashkinoy KV, editors. Moskva, Miklosh. 2009;1-432. Russian.
11. Puhlik BM. [Modern technologies for the treatment of allergic diseases]. Zdorove plyus. 2003;2:4-13. Russian.

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THE TREATMENT OF PATIENTS WITH ASTHMA AND COMORBIDITY

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Key words: *asthma, diabetes mellitus type 2, MCP-1, MMP-9, von Willebrand factor, L-arginine, Tiotropium bromide*
Ключевые слова*: бронхиальная астма, сахарный диабет 2 типа, MCP-1, MMP-9, фактор Виллебранда, L-аргинин, тиотропия бромид*

Abstract. The treatment of patients with asthma and comorbidity. Yeryomenko G.V., Bezditko T.V. *The increasing prevalence of asthma (A) and diabetes mellitus type 2 (DM2T) necessitates administration of the adequate antiasthmatic long-term basic therapy with consideration of comorbid states. The purpose consisted in revealing the therapeutic potential of Tiotropium bromide (TB) and L-arginine (Tivortine) in patients having uncontrolled moderately*

severe asthma in combination with DM2T (A+DM2T). Forty seven A+DM2T patients underwent an in-depth study before and after their treatment. They were divided into 2 groups: treatment (group 1, n=28) and comparison (group 2, n=19). Both groups received the standard 2-component therapy: budesonide/formoterol fumarate dihydrate – 160/4.5μg by 2 breaths twice a day and metformin at a dose of 500 mg twice a day. The complex of their basic therapy for group 1 additionally included TB (18 μg a day) and arginine hydrochloride preparation (Tivortine® aspartate, Yuriya-Farm) orally by 15 ml twice a day during 3 months (90 days). The patients were followed up 3 months and one year later. Their general condition demonstrated positive dynamics in both groups, the number of exacerbations in group 1 reducing by a factor of 4. The complex use of L-arginine and TB preparations against a background of the basic therapy in A+DM2T patients produced a better control over the disease, a more rapid elimination of obstruction manifestations, achievement and prolongation of the clinical spirographic remission, an improvement of the quality of life, correction of disturbances in haemocoagulation, fibrinolysis and the functional state of endothelium.

Реферат. Лечение больных бронхиальной астмой с коморбидностью. Ерёменко Г.В., Бездетко Т.В. *Растущая распространенность бронхиальной астмы (БА) и сахарного диабета 2 типа (СД2Т) обуславливает необходимость назначения адекватной противоастматической длительной базисной терапии с учетом коморбидных состояний. Целью исследования являлось определение терапевтического потенциала тиотропия бромида (ТБ) и L-аргинина (Тивортин) у больных при ассоциации БА среднетяжелого течения, неконтролируемой, в сочетании с СД2Т. Было углубленно обследовано 47 больных БА+СД2Т до и после лечения. Пациенты были разделены на 2 группы – основная группа (группа 1, n=28) и группа сравнения (группа 2, n=19). Обе группы больных получали стандартную 2-х компонентную терапию – будесонид/формотерола фумарата дигидрат – 160/4,5мкг по 2 вдоха дважды в сутки и метформина в дозе 500 мг 2 раза в сутки. Больным 1 группы в комплекс базисной терапии дополнительно были включены тиотропия бромид (18 мкг в сутки) и препарат аргинина гидрохлорид (Тивортин® аспартат «Юрия-Фарм» внутрь по 15 мл 2 раза в сутки, курс лечения – 3 мес. (90 дней)). Контрольный осмотр больных был назначен через 3 месяца и один год. Установлена положительная динамика в самочувствии больных в обеих группах, а количество обострений в группе 1 уменьшилось в 4 раза. Комплексное применение препаратов L-аргинина и тиотропия бромида на фоне базисной терапии у больных БА+СД2Т приводит к лучшему контролю над заболеванием, более быстрому устранению проявлений обструкции, достижению и увеличению продолжительности клинико-спирографической ремиссии, улучшению качества жизни, коррекции нарушений гемокоагуляции, фибринолиза и функционального состояния эндотелия.*

Treatment of comorbid states is one of important problems in medical practice. Ageing of population, bad habits, hypodynamia, irrational nutrition and a worsening ecological situation create conditions for a constant stress of the adaptive and biochemical mechanisms in the organism of the modern man with a resultant formation of several diseases in it. The prevalence of comorbid pathology in patients averages 78.6%, this condition occurring in 82% of cases in women and 72% in men [2]. The number of comorbid diseases in one patient considerably increases with age. For example, researchers have revealed that multimorbidity rises from 10% at the age, which does not exceed 19 years, to 80% in people at the age of 80 and older [14]. The simultaneous presence of several diseases affects each of them, aggravating their course, facilitating an earlier formation of complications and creating difficulties for therapy. The risk of death in case of two concomitant diseases is 5-10% and rises up to 70-80%, when their number increases up to five. Especially noteworthy is a combination of diseases, which have common or close aetiological and pathogenetic factors. The European standard of the GINA (2016 revision) for asthma contains a list of concomitant diseases, which can affect the course of the main pathology in a patient so much that the basic treatment is insufficient and becomes ineffective. Such diseases include rhinitis and rhinosinusitis, gastro-oesophageal reflux disease, night apnoea as well as diabetes mellitus and obesity [6, 19, 20].

It is possible to achieve the full or partial control of asthma (A) in the majority of patients under conditions of the correct assessment of its severity, the available level of asthma control and administration of the adequate antiasthmatic long-term basic therapy with consideration of comorbid states [21]. Pharmacotherapy is an essential component of treatment for any asthma. According to contemporary views on treatment of asthma, the main drugs for maintaining control over symptoms are provided by inhaled glucocorticosteroids (IGCS) with the personalized approach and attempts to separate single phenotypes of the disease with a subsequent development of the individual treatment plan (GINA, 2017) [15]. At present there is no need to prove advantages of combined therapy in fixed combinations of IGCS with long-acting β2agonists (LABA) over monotherapy with IGCS.

Active searches are constantly made for relationships between the phenotype, genotype, mechanisms of the disease development and appearance of

concomitant pathology, which may result from the therapy given. In future the above will make it possible to develop an algorithm for administering drugs depending upon the variant of the disease course [9, 20]. But it is believed that the most essential and clinically significant feature in the course of asthma in patients with diabetes mellitus type 2 (DM2T) consists in their overweight and obesity, thereby hindering the expected decrease of the disease severity in the process of treatment [19, 16]. Besides, the patients from this group demonstrate less efficiency of their basic therapy with use of IGCS; this fact often requires an increase in the daily dose of the used drugs with a resultant disturbance of carbohydrate metabolism [10, 13, 17]. In this connection it is necessary to study further the mechanisms of appearance of resistance to treatment and progression of asthma, combined with DM2T. The problem necessitates a multidimensional approach to diagnosis with inclusion of inflammatory markers, which are required for correction of the treatment.

Purpose – to reveal the therapeutic potential of Tiotropium bromide (TB) and L-arginine (Tivortine) in patients having uncontrolled moderately severe asthma in combination with DM2T (A+DM2T) on the basis of study of their influence on the functional state of lungs, the endothelial function and glucometabolic disturbances.

MATERIALS AND METHODS

The study involved 47 patients with A+DM2T before and after their treatment. The control group consisted of 20 apparently healthy people. The patients' diagnosis and treatment were made in compliance with Order No. 868 of the Ministry of Health of Ukraine dated October 8, 2013 "On Approval and Implementation of Medical-Technological Documents on Standardization of Medical Aid in Asthma" [8]. The diagnosis and treatment of concomitant DM2T were made by a skilled professional in endocrinology according to effective Ukrainian protocols [7]. The patients were divided into 2 groups: the treatment group (group 1, n=28) and the comparison group (group 2, n=19). Both groups of patients received the standard 2-component therapy: budesonide/formoterol fumarate dehydrate – 160/4.5 μg (IGCS+LABA) in a dry powder inhaler by 2 breaths twice a day and metformin at a dose of 500 mg 2 times a day. Salbutamol sulphate in a metered dose inhaler (100 μg "on demand") was used as an "emergency care" drug. The complex of their basic therapy for patients from group 1 additionally included TB (18 μg a day) and arginine hydrochloride preparation (Tivortine® aspartate, Yuriya-Farm) orally by 15 ml 2 times a day, the course of treatment lasted 3 months (90 days). The patients were followed up 3 months and one year later.

The patients' personal data included their gender, age, weight, body mass index (BMI) and history of exacerbations. On day 1 as well as after 3 and 12 months since the beginning of therapy the following examinations were made: forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), forced expiratory volume (FEV), Tiffeneau-Pinelli index (FEV_1/FVC), forced expiratory flow on the levels of 25, 50 and 75% (FEF25, FEF50, FEF75), as well as such general clinical and biochemical indices as glycated haemoglobin (HbAlc,%) and fasting blood glucose level (r) were analysed. The content of monocyte chemoattractant protein-1 (MCP-1) and matrix metalloproteinase-9 (MMP-9) in blood serum was determined by the method of enzyme immunoassay (ELISA) with help of "HUMAN MCP-1" and "HUMAN MMP-9"kits (eBioscience, Austria),von Willebrand factor (VWF) by the photoelectric colourimetric method [1] and nitric oxide metabolites, S-nitrosothiols (S-NO) by the spectrophotometric method modified by Koval'ova O.M. [4]. The state of external respiration (ER) was assessed on the basis of the forced respiration curve, which was registered on a SpiroCom spirograph (Ukraine). The following parameters were assessed: FVC, FEV1, FEF25, FEF50, FEF75. The assessment of the severity of asthma attacks and the level of the disease control was formalized and made according to the Asthma Control Questionnaire (ACQ) [11] and Asthma Quality of Life Questionnaire (AQLQ) [8]. The study findings were statistically processed with use of SPSS 19 program for Windows (IBM, USA). Quantitative variables were described by the following parameters: the median (Me) and the $25^{th}$and 75^{th}percentiles (Me [25%-75%]). In order to reveal differences between independent samples, the Mann-Whitney U test was used. The normality of data distribution was analysed with help of the Shapiro-Wilk test.

RESULTS AND DISCUSSION

Analysis of the findings revealed that after 12 months of the regular taking of the IGCS/LABA combination most of the ER indices in the examined groups tended to improve. But for the majority of characteristics these changes were not statistically significant (Fig. 1). Values of inflammatory markers in patients from group 1 decreased: MCP-1 from 806.14 [768.36-904.37] ng/ml to 534.50 [430.71-631.70] ng/ml (p=0.013), MMP-9 from 788.5 [336.14-933.31] ng/ml to 576.50 [343.2-645.74] ng/ml

(p=0.001); the above was accompanied with an improvement of the endothelial function: a reduction of VWF (Fig. 2) and an elevation of S-NO (Fig. 3). At the same time, there were no reliable changes of these indices in patients from group 2 (Figs. 4 and 5). Such a reduction of VWF as a decrease of the vasospastic state of endothelium under the effect of Tivortine and TB was revealed. At the same time, especially noteworthy is an increased content of nitric oxide metabolites (S-nitrosothiols) as indicators of functioning of vasodilatory mechanisms of cellular interactions. The latter fact can be regarded as the compensatory intensification of vasodilatory activity in response to a reduced action of VWF. Results of analysis of carbohydrate metabolism reliably demonstrated decreases of HbAlc% (from 7.50 [7.07-7.90]% to 6.3[5.95-6.72]%, p=0.01) and the glycaemic load level (from 6.90 [6.02-7.40] mmol/l to 6.01[5.20-6.61] mmol/l, p=0.03) in patients from group 1 and absence of reliable changes in group 2. The number of A+DM2T exacerbations during 12 months of follow-up was calculated on the basis of personal encounters of the patients and data of analysis of medical documents. Under the influence of the chosen treatment the number of exacerbations in group 1 decreased by a factor of 4 (down to [1.0-2.0] cases a year), and these changes were reliable (p=0.001). In group 2, on the contrary, this index improved but remained unreliable, it causing involvement into the study from 4.0 [4.0-5.0] cases a year to 3.0 [2.5-4.5] cases a year (p=0.607). The quality of life in patients from groups 1 and 2 improved (respectively, the general quality of life by 46% and 29%, the physical component of health by 34% and 18%, the mental component of health by 46% and 21%), the degree of asthma control increasing in patients from group 1 by 21% and in patients from group 2 by 12% by ACQ data. Analysis of anthropometric data changes showed a decrease of BMI in group 1 from 28.5 [26.7-32.5] kg/m^2 to 27.01 [24.59-30.3] kg/m^2, (p=0.001).

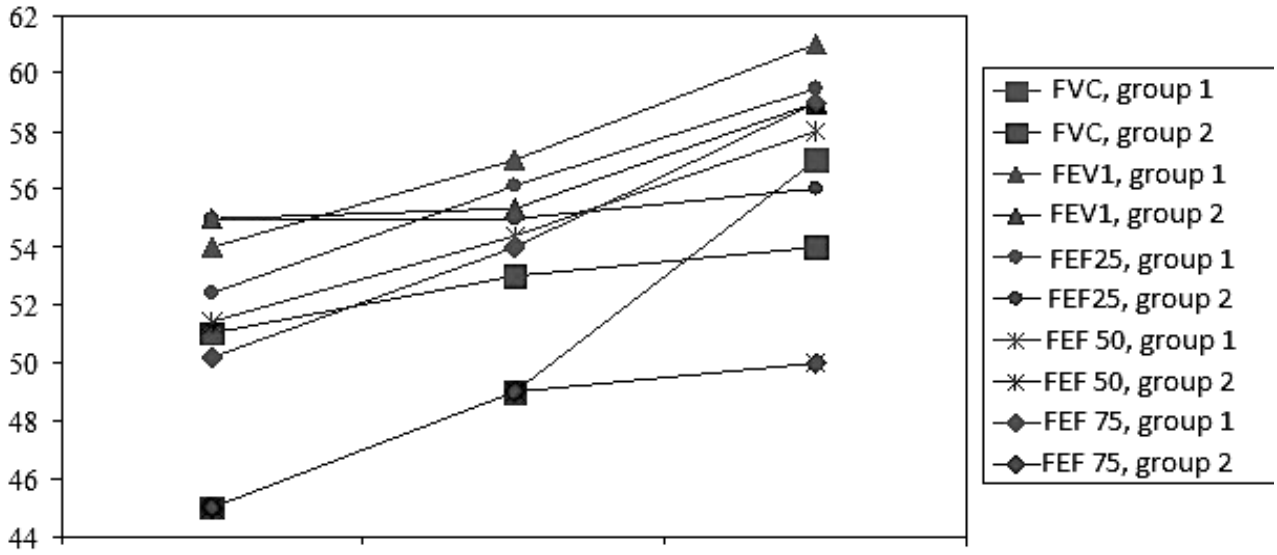

Fig. 1. The dynamics of changes in ER under the effect of treatment

The findings clearly demonstrate that it is reasonable to administer the combination of L-arginine and TB against a background of the basic therapy to patients with A+DM2T for reducing a possibility of exacerbations and improving the prognosis for the course of the disease [12, 18, 21].

It is known that the use of Tivortine in treatment of patients produces an effect on the endothelial function and improves its state, catalyzes the synthesis of nitric oxide in endotheliocytes, increases the level of cyclic guanosine monophosphate (cGMP) in vascular endothelium, decreases activation and adhesion of leukocytes and thrombocytes to vascular endothelium and inhibits the synthesis of MCP-1 [3, 5, 6].

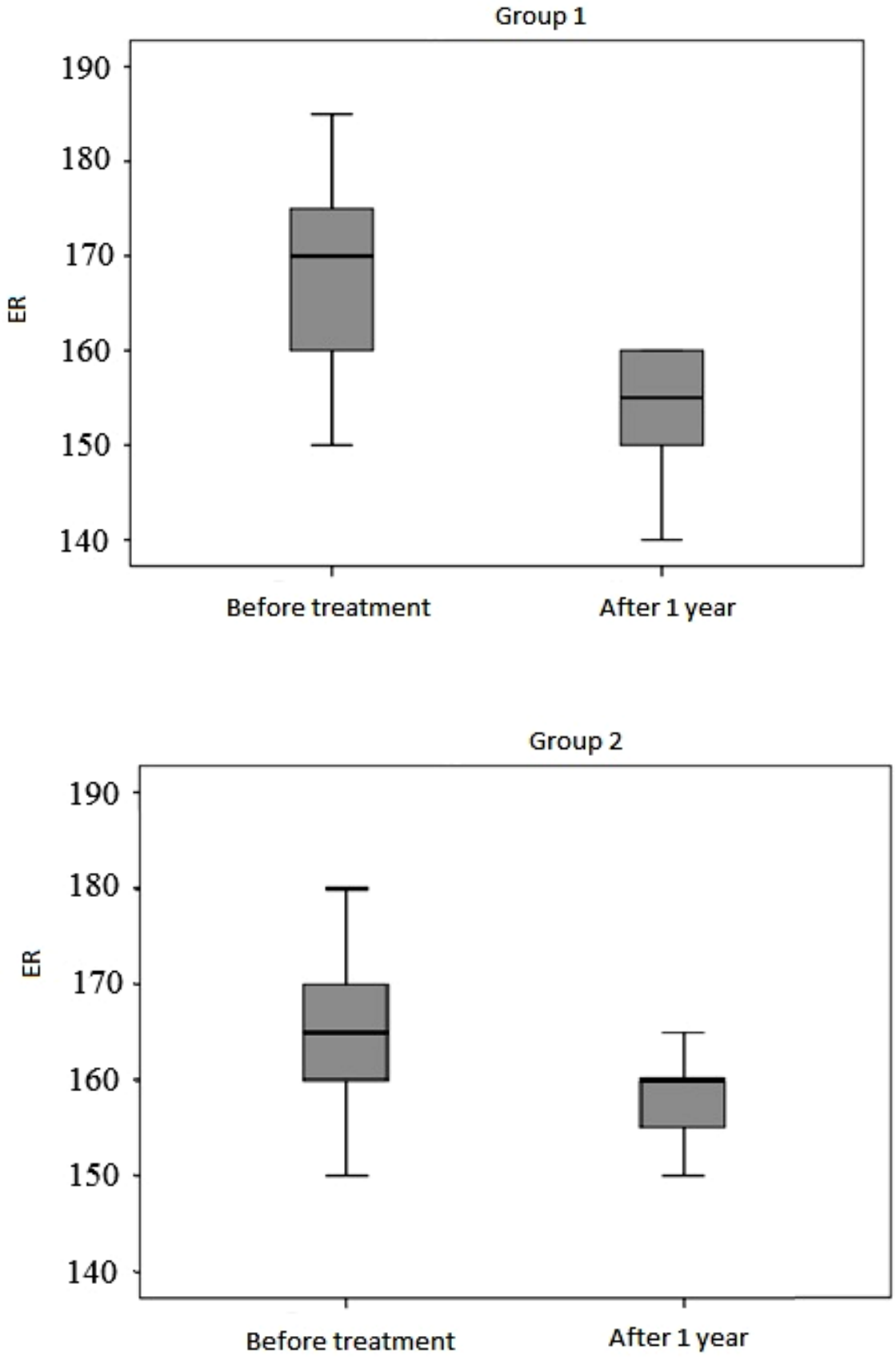

Fig. 2. The dynamics of changes in VWF under the effect of treatment (%)

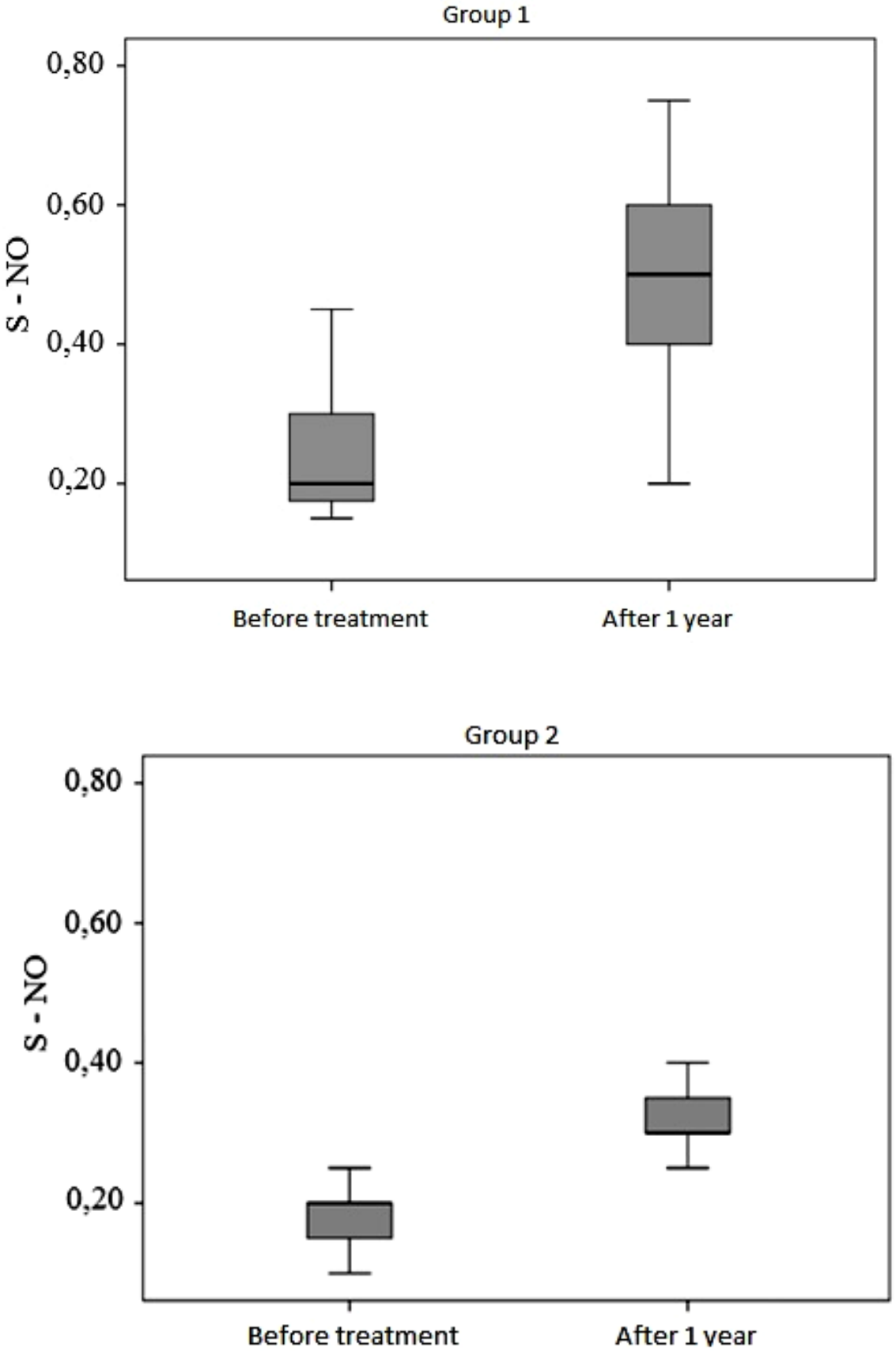

Fig. 3. The dynamics of changes inS-NO under the effect of treatment (µmol/l)

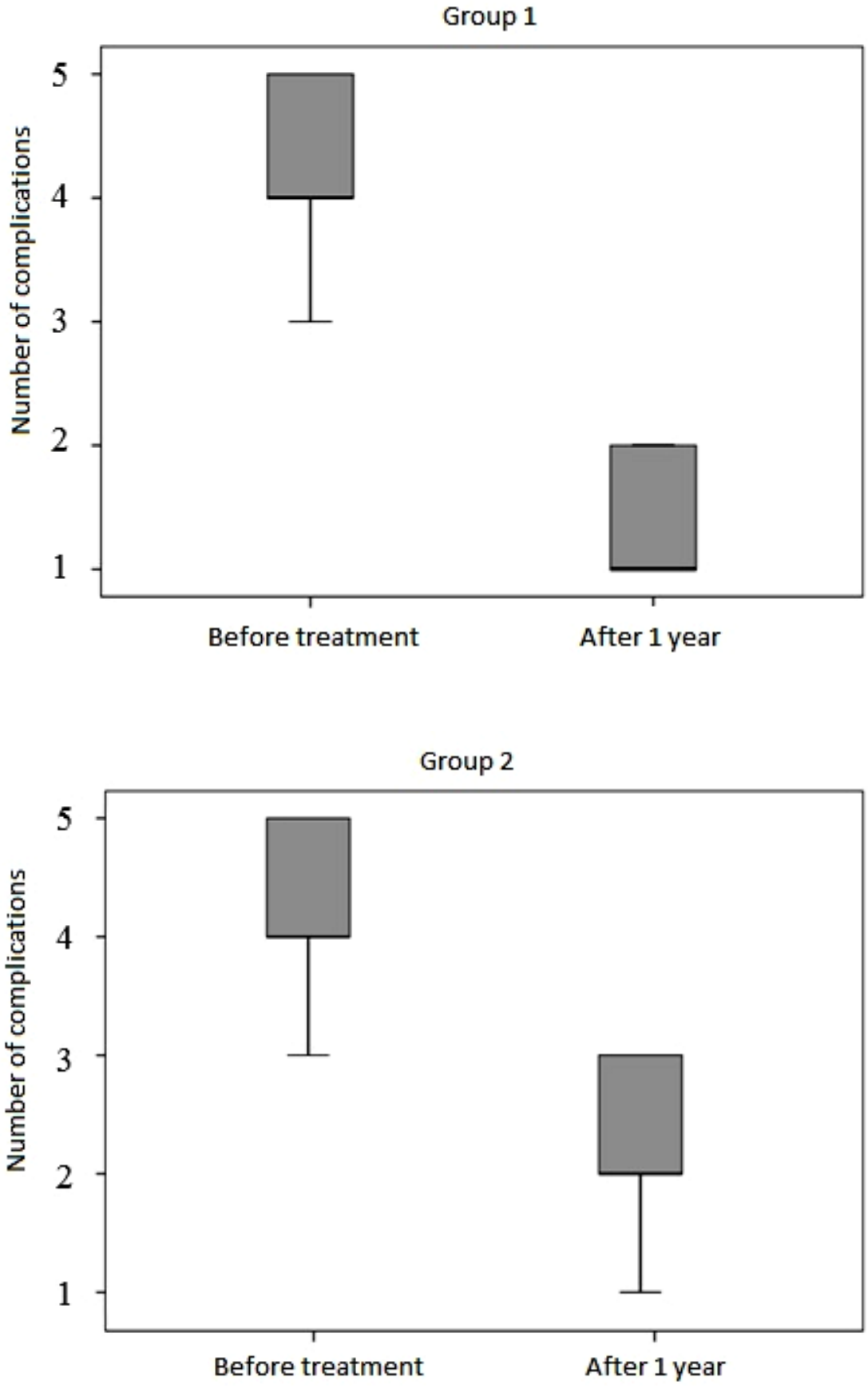

Fig. 4. The dynamics of the number of complications per year under the effect of treatment

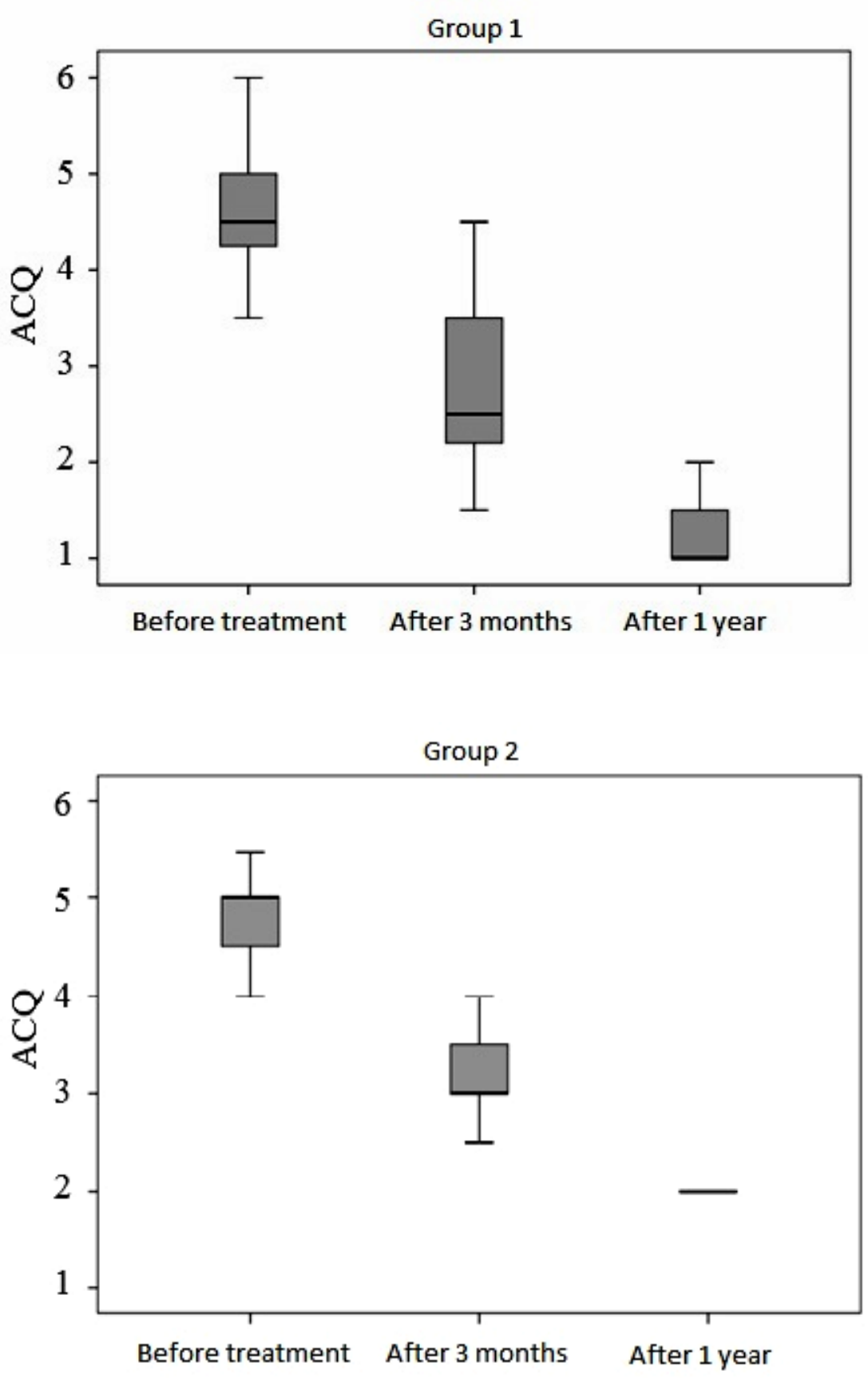

Fig. 5. The dynamics of ACQ under the effect of treatment

CONCLUSIONS

1. The complex use of L-arginine and TB preparations against a background of the basic therapy in patients with asthma combined with DM2T resulted in correction of disturbances in haemocoagulation, fibrinolysis and the functional state of endothelium with a better control over the disease.
2. When treating patients with asthma combined with DM2T it is reasonable to include L-arginine and TB preparations into the complex therapy due to the positive effect on the patients' general condition, a more rapid elimination of obstruction manifestations, achievement and prolongation of the clinical spirographic remission, and an improvement of the quality of life.
3. Comparison of the patients' indices from groups 1 and 2 before the treatment, after 3 months and after 1 year.

REFERENCES

1. Barkagan ZS, Momot AP. [Diagnosis and Controlled Therapy of Homeostatic Disorders]. Moskva, N′iudiamed; 2008. Russian.
2. Vertkin AL, Hovasova NO. [Comorbidity is a new pathology. The technology of its prevention and treatment]. The Archives of Internal Medicine. 2013;4:68-72. Russian.
3. Katerenchuk IP. [Optimization of the correction of endothelial dysfunction in patients with metabolic syndrome in the practice of a family doctor]. Liki Ukraïni. 2014;7/8:43-46. Ukrainian.
4. Koval'ova OM, Gorbach TV, Demydenko GV. [Diagnosis of endothelial function, assessment of vasoactive nitrogen oxide pool]. Kyiv; 2009. Russian.
5. Kuriata AV, Syrenko OJu. [Insulin resistance and endothelial dysfunction in patients with arterial hypertension in combination with rheumatoid arthritis and their correction with L-arginine aspartate]. Therapy. Ukrainskiy meditsinskiy vestnik. 2015;5:57-58. Russian.
6. Pertseva TA. [Features of treatment of patients with bronchial obstructive diseases in combination with diabetes and obesity]. Ukraïns'kiy pul'monologichniy zhurnal. 2017;2:59. Russian.
7. [Order of the Ministry of Health of Ukraine N 1118 of 21.12.2012 "On Approval and Implementation of Medical-Technological Documents for the Standardization of Medical Aid in Type 2 Diabetes"]. [Internet]. Ministry of Health of Ukraine; 2012. Available from: http://old.moz.gov.ua/ua/portal/dn_20121221_1118.html
8. [Order of the Ministry of Health of Ukraine N 868 of 10.08.2013 "On Approval and Implementation of Medical-Technical Documents on Standardization of Medical Aid in Bronchial Asthma"]. [Internet]. Ministry of Health of Ukraine; 2013. Available from: http://old.moz.gov.ua/ua/portal/dn_20131008_0868.html
9. Feshchenko JuI. [Asthma, chronic obstructive pulmonary disease: promising global strategy of management, advanced diagnostic techniques, modern approaches to therapy]. Astma ta alergiya. 2015;4:36-42. Ukranian.
10. Al-Shawwa B, Al-Huniti NH, DeMattia L, Gershan W. Asthma and insulin resistance in morbidly obese children and adolescents. J Asthma. 2007;44(6):469-73.
11. Pereira ED, Cavalcante AG, Pereira EN, Lucas P, Holanda MA. Asthma control and quality of life in patients with moderate or severe asthma. J Bras Pneumol. 2011;37(6):705-11.
12. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma: From bronchoconstriction to airways inflammation and remodeling. Am J RespirCritCareMed. 2000;161(5):1720-45.
13. Barnes PJ. Corticosteroid resistance in patients with asthma and chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2013;131(3):636-45
14. Campbell-Scherer D. Multimorbidity: a challenge for evidence-based medicine. EvidBasedMed. 2010;15:165-6.
15. Global strategy for asthma management and prevention. Bethesda: National Institutes of Health National Heart & Lung and Blood Institute. 2017;159.
16. Thuesen BH, Husemoen LLN, Hersoug LG, Pisinger C, Linneberg A. Insulin resistance as a predictor of incident asthma-like symptoms in adults. ClinExp Allergy. 2009;39(5):700-7.
17. Juel CT-B, Ulrik CS. Obesity and asthma: impact on severity, asthma control, and response to therapy. Respir Care. 2013;58(5):867-73.
18. Rashid Q, Klein R. Tiotropium in the treatment of patients with asthma. South Med J. 2014;107(5):330-7.
19. Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. Am J Med. 2010;123(11):1001-6.
20. Tesse R, Schieck M, Kabesch M. Asthma and endocrine disorders: Shared mechanisms and genetic pleiotropy. MolCellEndocrinol. 2011;333(2):103-11.
21. Kerstjens HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy. N Engl J Med. 2012;367(13):1198-207.

СПИСОК ЛІТЕРАТУРИ

1. Баркаган З.С. Диагностика и контролируемая терапия нарушений гомеостаза / З.С. Баркаган, А.П. Момот. – Москва: Ньюдиамед, 2008. – 292 с.
2. Верткин А.Л. Коморбидность – новая патология. Технология ее профилактики и лечения /

А.Л. Верткин, Н.О. Ховасова // Архив внутренней медицины. – 2013. – № 4. – С. 68-72.

3. Катеренчук І.П. Оптимізація корекції ендотеліальної дисфункції у пацієнтів з метаболічним синдромом у практиці сімейного лікаря / І.П. Катеренчук // Ліки України. – 2014. – № 7/8. – С. 43-46.

4. Ковалева О.М. Диагностика эндотелиальной функции-оценка вазоактивного пула оксида азота / О.М. Ковалева, Т.В. Горбач, Г.В. Демиденко. – Киев, 2009. – 19 с.

5. Курята А.В. Инсулинорезистентность и эндотелиальная дисфункция у больных с артериальной гипертензией в сочетании с ревматоидным артритом и их коррекция L-аргинина аспартатом / А.В. Курята, О.Ю. Сиренко // Therapia = Укр. мед. вестник. – 2015. – № 5. – С. 57-58.

6. Перцева Т.А. Особенности лечения пациентов с бронхообструктивными заболеваниями в сочетании с сахарным диабетом и ожирением / Т.А. Перцева // Укр. пульмонол. журнал. – 2017. – № 2. – С. 59.

7. Про затвердження та впровадження медико-технологічних документів зі стандартизації медичної допомоги при цукровому діабеті 2 типу: Наказ МОЗ України № 1118 від 21.12.2012 р. [Електронний ресурс] / МОЗ України. – Режим доступу: http://old.moz.gov.ua/ua/portal/dn_20121221_1118.html

8. Про затвердження та впровадження медико-технічних документів зі стандартизації медичної допомоги при бронхіальній астмі: Наказ МОЗ України № 868 від 08.10.2013 р. [Електронний ресурс] / МОЗ України. – Режим доступу: http://old.moz.gov.ua/-ua/portal/dn_20131008_0868.html

9. Фещенко Ю.І. Бронхіальна астма, хронічне обструктивне захворювання легень: перспективна глобальна стратегія ведення, новітні методики діагностики, сучасні підходи до терапії / Ю.І. Фещенко // Астма та алергія. – 2015. – № 4. – С. 36-42.

10. Asthma and insulin resistance in morbidly obese children and adolescents / B.A. Al-Shawwa, N.H. Al-Huniti, L. DeMattia, W. Gershan // The Journal of Asthma: official journal of the Association for the Care of Asthma. – 2007. – Vol. 44, N 6. – P. 469-473. doi: 10.1080/02770900701423597

11. Pereira E.D.B. Asthma control and quality of life in patients with moderate or severe asthma / E.D.B. Pereira, A.G. de M. Cavalcante, E.N.S. Pereira [et al.] // J. Brasileiro de Pneumologia:publicaçãooficial da SociedadeBrasileira de Pneumologia e Tisiologia. – Vol. 37, N 6. – P. 705-711.

12. Asthma: from bronchoconstriction to airways inflammation and remodeling / J. Bousquet, P.K. Jeffery, W.W. Busse [et al.]. – 2000. doi: 10.1164/ajrccm.161.5.9903102

13. Barnes P.J. Corticosteroid resistance in patients with asthma and chronic obstructive pulmonary disease / P.J. Barnes // J. Allergy Clin. Immunol. – 2013. – Vol. 131, N 3. – P. 636-645. doi: 10.1016/j.jaci.2012.12.1564

14. Campbell-Scherer D. Multimorbidity: a challenge for evidence-based medicine / D. Campbell-Scherer // Evidence-Based Medicine. – 2010. – Vol. 15, N 6. – P. 165-166. doi: 10.1136/ebm1154

15. Global strategy for asthma management and prevention / National Institutes of Health: National Heart, Lung and Blood Institute. – Bethesda, 2017. – 159 p.

16. Insulin resistance as a predictor of incident asthma-like symptoms in adults / B.H. Thuesen, L.L.N. Husemoen, L.G. Hersoug [et al.] // Clinical and Experimental Allergy. – 2009. = Vol. 39, No. 5. – P. 700-707. doi: 10.1111/j.1365-2222.2008.03197.x

17. Juel C.T.-B. Obesity and asthma: impact on severity, asthma control, and response to therapy / C.T.-B. Juel, C.S. Ulrik // Resp. Care. – 2013. – Vol. 58, N 5. – P. 867-873. doi: 10.4187/respcare.02202

18. Rashid Q. Tiotropium in the treatment of patients with asthma / Q. Rashid, R. Klein. – 2014. doi: 10.1097/SMJ.0000000000000108

19. Suissa S. Inhaled corticosteroids and the risks of diabetes onset and progression / S. Suissa, A. Kezouh, P. Ernst // Am. J. Med. – 2010. – Vol. 123, N 11. – P. 1001-1006. doi: 10.1016/j.amjmed.2010.06.019

20. Tesse R. Asthma and endocrine disorders: shared mechanisms and genetic pleiotropy / R. Tesse, M. Schieck, M. Kabesch. – 2011. doi: 10.1016/j.mce.2010.11.032

21. Tiotropium in asthma poorly controlled with standard combination therapy / H.A.M. Kerstjens, M. Engel, R. Dahl [et al.] // New Engl. J. Med. – 2012. – Vol. 367, N 13. – P. 1198-1207. doi: 10.1056/NEJMoa1208606