**Fadieieva G.** ***Comparative influence of body mass index on response to asthma therapy / G. Fadieieva, L. Pristupa, O. Pogorielova, T. Mazur // British Journal of Science, Education and Culture. – 2014. – 1 (5). – P. 185-190***

*Fadieieva Ganna, Sumy State University,*
*Assistant of Professor, Medical Institute, Chair of Internal Medicine,*
*E-mail: a0408@rambler.ru*
*Prystupa Lyudmyla, Sumy State University,*
*Professor, Doctor of Medical Sciences, Medical Institute, Chair of Internal Medicine,*
*Pogorelova Oksana, Sumy State University,*
*Assistant of Professor, Medical Institute, Chair of Internal Medicine,*
*Mazur Tatyana, Sumy State University,*
*Student of the 4th year, Medical Institute, Chair of Internal Medicine.*

## *Comparative influence of body mass index on response to asthma therapy*

**Abstract:** Asthma in obese patients accompanies by hyperleptinemia that promotes systemic violations of cytokine regulation, excessive synthesis of strong bronchoconstrictors – cysteinyl leukotrienes. The addition of quercetin to budesonide combined with formoterol improves results of anti-inflammatory standard treatment in obese asthma patients, makes it possible to achieve asthma-control and maintain it in the majority of patients.

**Keywords:** asthma, obesity, leptin, cysteinyl leukotrienes, quercetin.

The prevalence of both obesity and asthma have increased in recent decades. Several studies have shown that overweight and obesity is associated with more severe asthma (limitations in daily activities, breathlessness and wheezing, use of rescue medication, emergency department visits) and impaired quality of life, compared with normal weight individuals [1]. There are several mechanisms that may explain relationship between obesity and asthma. Obesity causes airflow limitation, with reduction of both forced expiratory volume in one second ($FEV_1$) and forced vital capacity (FVC) [2]. Many mediators are synthesized and secreted

by cells from adipose tissue: interleukin (IL)-6, IL-10, eotaxin, tumor necrosis factor (TNF)-α, C-reactive protein, leptin, adiponectin, etc. Leptin is an important immunoregulatory hormone since it enhances a number of immune responses, including macrophage effector functions, cytokine synthesis [4, 5], and T helper (Th) cell polarization to a $Th_1$ phenotype [6]. Thus obesity also leads to a state of low-grade systemic inflammation that may act on the lung to exacerbate asthma.

Mancuso P. et al. found that leptin pretreatment of either rat alveolar or murine peritoneal macrophages for 16 h dose dependently increased the synthesis of leukotriene B4 and cysteinyl leukotrienes (LT) [**7**]. Cysteinyl-LTs are the most potent endogenous bronchoconstrictors and also important regulators of inflammatory cytokine production, via regulation of IL-10 production and in vivo differentiation of T cells [8]. Cysteinyl-LT-induced activation of human monocytes and dendritic cells may be specifically inhibited by IL-10, suggesting a direct link between the 5-lipoxygenase proinflammatory pathway and IL-10 regulatory mechanisms [9].

Overweight and obesity is associated with less favorable response to asthma therapy, with regard to symptoms, level of $FEV_1$, fraction of exhaled nitric oxide, and airway responsiveness [10, 11]. Some studies suggest that asthma in the obese patient might be more responsive to leukotriene modifiers, than to inhaled corticosteroids (ICS) [12]. An alternative drug that inhibits the activity of 5-lipoxygenase and phospholipase A2 reducing the production of LTs is bioflavonoid - quercetin [13]. Supressing nuclear factor-kappa (NF-κβ), which regulates the expression of various proinflammatory cytokines, quercetin reduces the production of IL-1β, TNF-α, IL-6, IL-8, IL-4, IL-13, stabilizing membranes of mast cells and basophils, blocking histamine out [14-18], inhibits monocyte chemoattractant protein synthesis by airway epithelium [19].

OBJECTIVES: Our aim was to assess the impact of obesity on asthma control, biomarkers of inflammation and response to therapy in asthma patients.

METHODS: Achievement of asthma control as defined by the global initiative on asthma guidelines (GINA) was examined in 160 asthmatic patients

using ICS. Spirometry was performed using a standard spirometer. Height and weight were measured and body mass index (BMI) was calculated. We measured sagittal abdominal diameter (SAD) and calculated the amount of visceral fat (AVF) by the formula: AVF = 0,731* SAD (cm) - 11,5.

Inclusion criteria: Males and females aged 18-60 years with a 1-yr history of clinical symptoms of asthma with normal (BMI<25.0 kg/$m^2$) weight or obesity (BMI≥30.0 kg/$m^2$). Patients' asthma treatment could include ICS at the time of randomization. Patients were eligible for randomization if they had a $FEV_1$>40% and <80% of the predicted value at rest and at least a 15% increase in $FEV_1$ after ß-agonist administration. Patients were nonsmokers. Exclusion criteria: severe asthma exacerbation that require systemic corticosteroid, subjects with clinically significant disease of any organ system that would confound the interpretation of the results (including diabetes mellitus).

After examination and consideration of inclusion/exclusion criteria 132 eligible patients with moderate to severe asthma were divided into two groups according to their BMI. Group I: 24 normal weight patients (mean: age 42,3±2,32 years; duration of disease 18,0±1,70 years; BMI 23.5+/-1.25 kg/$m^2$). Group II: 108 obese patients with mean age 47,1±0,74 years; duration of disease 16,6±0,89 years; BMI 34.1+/-0.34 were randomized into 2 subgroups – II-a and II-b. Number of patients with moderate or severe asthma were equal at each group.

Patients of the I and II-a group received combination of inhaled budessonide and long-acting inhaled $ß_2$-agonist – formoterol, patients of the II-b group – budesonide in combination with formoterol and quercetin (500 mg iv for 5 days, then 240 mg per os daily). Patients with moderate asthma received 200 μg of inhaled budesonide b.i.d. and 12 μg of formoterol, patients with severe asthma received 400 μg of inhaled budesonide b.i.d. and 12 μg of formoterol. Treatment period lasted 3 month.

Fasting serum leptin, cysteinyl-LTs, IL-6, IL-10, TNF-α concentrations were measured in blood serum of 80 study patients by enzyme-linked immunosorbent assay (ELISA).

Statistical analysis of the results was performed according to the method of variation statistics using the licensed Microsoft Excel. Research values are presented as the sample mean, sample standard deviation. Assessment of differences between mean values of independent samples was performed by parametric method for determining the statistical significance of the difference of two sets of observations using the Student` and Fisher` method: calculated t value, was compared with tabulated values. The relations between two variables were calculated with Spearman's correlation test. A p value <0.05 was considered to indicate statistical significance.

RESULTS: The prevalence of obesity in our study's population is 36,7%.

Obese subjects more frequently reported ß$_2$-agonist use (4,9±0,17 vs. 3,9±0,37, p<0,05) and nocturnal awakenings (1,8±0,08 vs. 1,3±0,13, p<0.05) in the previous 2 months than normal-weight subjects. In baseline airway function assessment we revealed that median $FEV_1$ % pred and FVC was (59,8±2,10)% and (67,4±1,80)%, respectively for patients of normal weight, (55,0±1,01)% and (59,1±1,02)%, respectively for patients who were obese. $FEV_1$ was negatively associated with BMI (r=-0,23; p<0,05), but more closely with AVF (r=-0,30, p<0,05).

Asthma severity at baseline was greater for obese individuals, as shown by their lower $FEV_1$ (% pred) and greater daily use of ß$_2$-agonist.

Presence of systemic inflammation associated with obesity with elevated levels of circulating mediators is shown in table 1.

Table 1. Levels of circulating mediators in asthma patients.

| Parameter | Groups of patients | | |
|---|---|---|---|
| | Control, n = 20 | Group I (with normal BMI), n = 22 | Subgroup II-a (with obesity), n = 29 |
| Leptin, ng/ml | 4,9 ± 0,54 | 14,9 ± 0,75 * | 35,8 ± 2,15** * |
| TNF-α, pg/ml | 24±3,2 | 75±7,31* | 204±11,5**  * |

| | | | |
|---|---|---|---|
| IL-6, pg/ml | 4,3 ± 0,31 | 11,3 ± 0,38* | 24,2 ± 1,95** * |
| Cysteinyl LTs, pg/ml | 66,8 ± 7,95 (n=12) | 258,5 ± 27,58* | 340,7 ± 26,54* ** |
| IL-10, pg/ml | 4,1 ± 0,43 | 12,9 ± 1,28* | 9,2 ± 1,11** * |

Notes:

1.* - Statistical significance of differences ($p<0,05$) compared to the control;

2. ** - Statistical significance of differences ($p<0,05$) compared with group I.

At admission asthmatic patients with obesity had higher mean levels of serum leptin, TNF-α, IL-6, cysteinyl LTs than normal weight patients and vs control group measurements ($p<0,05$). IL-10 concentration was increased in both groups. BMI correlated significantly with leptin ($r=0,78$, $p<0,05$), TNF-α ($r=0,66$, $p<0,05$), IL-6 ($r=0,64$, $p<0,05$) concentrations. Leptin strongly correlated with TNF-α ($r=0,52$, $p<0,05$), IL-6 levels ($r=0,69$; $p<0,05$). Serum cysteinyl-LT levels correlated with BMI ($r=0,38$; $p<0,05$), $FEV_1$($r=0,50$; $p<0,05$), leptin level ($r=0,35$; $p<0,05$), IL-10 ($r =-0,42$; $p<0,05$).

Thus asthma in obese patients accompanies by hyperleptinemia that promotes systemic violations of cytokine regulation, excessive synthesis of strong bronchoconstrictors – LTs.

After budesonide-formoterol treatment for 3 month we revealed that nocturnal awakening and $ß_2$-agonist use decreased to (0,2±0,08) and (0,7±0,19), respectively ($p<0,05$) in the patients of the I group vs (0,9±0,07) and (1,9±0,08), respectively in the patients of the II-a group ($p<0,05$). $FEV_1$ and FVC increased to (77,7±1,19)% and (75,6±1,09)%, respectively in the patients of the I group vs (63,9 ± 1,52)% and (59,8 ± 1,20)%, respectively in the patients of the II-a group. In patients with asthma, serum leptin, IL-6, TNF-α, cysteinyl LTs levels were decreased, IL-10 was increased. Levels of circulating mediators in 3 month period of treatment is shown in the table 2.

Maintenance of a high leptin, IL-6, cysteinyl LTs content after basic treatment with budesonide-formoterol in obese asthma patients leads to persistent inflammation in the bronchi explaining long-term saving of obstructive disorders

and justifies the feasibility of the additional use of antileukotrien drugs for elimination of identified systemic cytokine-leukotrien imbalance.

After 3 month of budesonide-formoterol and quercetin administration we revealed that nocturnal awakening and ß$_2$-agonist use decreased to (0,3±0,08) and (0,9±0,09), respectively, $FEV_1$ and FVC increased to (70,4±1,26) % and (62,8± 1,21) %, respectively in the patients of the II-b group and therefore contributing to decline obstructive disorders compared with the patients of the II-a group who received just budesonide-formoterol ($p<0.05$).

Table 2. Levels of circulating mediators in asthma patients in 3 month period of treatment

| Parameter | Groups of patients | | | |
|---|---|---|---|---|
| | Control, n = 20 | Group I, n = 22 | Group II-a, n = 29 | Group II-b, n = 29 |
| Leptin, ng/ml | 4,9 ± 0,54 | 9,8 ± 0,54* | 32,3 ± 2,11* | 32,1 ± 1,94*** |
| TNF-α, pg/ml | 24±3,2 | 42±4,54* | 130±19,52* | 78±18,62***** |
| IL-6, pg/ml | 4,3 ± 0,31 | 6,8 ± 0,38* | 17,8 ± 1,74* | 12,3 ± 1,22***** |
| Cysteinyl LTs, pg/ml | 66,8 ± 7,95 (n=12) | 147,7±12,79* | 268,8±18,91* | 187,0±23,4***** |
| IL-10, pg/ml | 4,1 ± 0,43 | 22,2 ± 1,87* | 16,5 ± 1,49* | 20,8 ± 1,45***** |

Notes:

1.* - Statistical significance of differences ($p<0.05$) compared to the control;

2. ** - Statistical significance of differences ($p<0.05$) compared with group I;

3. * - Statistical significance of differences ($p<0.05$) compared with group II-a.

The addition of quercetin to budesonide-formoterol was statistically superior to budesonide-formoterol for obese subjects for ß$_2$-agonist use, $FEV_1$ ($p<0,05$), levels of pro- and anti-inflammatory mediators, except leptin concentrations ($p< 0,05$). The addition of quercetin makes it possible to improve results of anti-inflammatory standard treatment in obese asthma patients.

Of patients with normal weight, (58,3±10,3)% achieved asthma-control compared with (9,2±3,9)% of patients who were obese ($p<0,05$). Of obese patients, (24,1±5,8)% achieved asthma-control after 3 month of budesonide-formoterol with quercetin treatment compared with (9,2±3,9)% of patients who were used just budesonide-formoterol inhalations ($p<0,05$). Partly controlled asthma was revealed in (41,7±10,3)% of normal weight patients, (63,0±6,6)% of patients of the II-a group and (64,8±6,6)% - of the II-b group ($p>0,05$). Asthma course remained uncontrolled in (27,8±6,2)% of patients from the II-a group and (11,1±4,3)% - of the II-b group ($p<0,05$).

CONCLUSIONs: Obesity is associated with poorer asthma control: obese asthma patients demonstrated more usage of $ß_2$-agonists and more significant obstructive disturbances in lung function.

Persistent hyperleptinemia in obese asthma patients contributes to increased synthesis of cysteinyl-LTs, IL-6, TNF-α, reduced production of IL-10, and as a result – reduced response to ICS.

The influence of BMI on response to combined treatment with quercetin was different from that observed for budesonide-formoterol: treatment in combination with quercetin resulted in improvement in asthma control in obese individuals due to significant reduction in serum cysteinyl-LTs, IL-6, TNF-α, and increase in serum IL-10.

References:

1. Akerman M.J.H., Calcanis C.M., Madsen M.K. Relationship between asthma severity and obesity // J. Asthma, 2004. – Vol. 41(5). – P.521-526.

2. Sin D.D., Jones R.L., Man S.F. Obesity is a risk factor for dyspnea but not for airflow obstruction // Arch. Intern. Med, 2002. – Vol. 162. – P. 1477–1481.

3. Weisberg S.P., McCann D., Desai M. et al. Obesity is associated with macrophage accumulation in adipose tissue // J. Clin. Invest., 2003. – Vol. 112. – P. 1796-1808.

4. Loffreda S., Yang S., Lin H. et al. Leptin regulates proinflammatory immune responses // FASEB J., 1998. – Vol. 12. – P. 57–65.

5. van Dielen F.M. Increased leptin concentrations correlate with increased concentrations of inflammatory markers in morbidly obese individuals // Int.J. Obes.Relat.Metab.Disord., 2001. – Vol. 25(12). – P. 1759-1766.

6. Lord G.M., Matarese G., Howard J.K. et al. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression // Nature, 1998. – Vol. 394. – P. 897–901.

7. Mancuso P. et al. Leptin augments alveolar macrophage leukotriene synthesis by increasing phospholipase activity and enhancing group IVC iPLA2 (cPLA2gamma) protein expression // Am. J. Physiol. Lung Cell Mol. Physiol., 2004. – Vol. 287, № 3. – P. 497–502.

8. DiMeo D. Increased interleukin-10 production and Th2 skewing in the absence of 5-lipoxygenase // Immunology, 2008. – Vol. 123(2). – P. 250-262.

9. Woszczek G. et al. IL-10 inhibits cysteinyl leukotriene-induced activation of human monocytes and monocyte-derived dendritic cells // J. Immunol., 2008. – Vol. 180, № 11. – P. 7597–7603.

10. Rodrigo G.J., Plaza V. Body mass index and response to emergency department treatment in adults with severe asthma exacerbations: a prospective cohort study // Chest, 2007. – Vol. 132(5). – P.1513-1519.

11. Camargo C.A. Jr, Boulet L.P., Sutherland E.R. et al. Body mass index and response to asthma therapy: fluticasone propionate/salmeterol versus montelukast. J Asthma, 2010. – Vol. 47(1). – P. 76-82.

12. Peters-Golden M., Swern A., Bird S.S. et al. Influence of body mass index on the response to asthma controller agents // Eur. Respir. J., 2006. – Vol.27. – P. 495–503.

13. Пархоменко А. Н. и др. Первый опыт применения внутривенной формы ингибитора 5-липоксигеназы у больных с острым инфарктом миокарда: клинико-гемодинамические параллели, влияние препарата на размеры некроза // Український кардіологічний журнал, 2000. – № 1-2. – С. 5 – 9.

14. Kawai M. et al. Flavonoids and related compounds as anti-allergic substances // Allergol. Int., 2007. – Vol. 56, № 2. – P.113–123.

15. Park H. et al. Flavonoids inhibit histamine release and expression of proinflammatory cytokines in mast cells // Arch. Pharm. Res., 2008. – Vol. 31, № 10. – P. 1303–1311.

16. Kempuraj D. et al. Inhibitory effect of quercetin on tryptase and interleukin-6 release, and histidine decarboxylase mRNA transcription by human mast cell-1 cell line // Clin. Exp. Med., 2006. – Vol. 6, № 4. – P.150–156.

17. Min Y.D., Choi C.H., Bark H. et al. Quercetin inhibits expression of inflammatory cytokines through attenuation of NF-kappaB and p38 MAPK in HMC-1 human mast cell line // Inflamm.Res., 2007. – Vol. 56(5). – P. 210-215.

18. Liu J., Li X., Yue Y. et al. The inhibitory effect of quercetin on IL-6 production by LPS-stimulated neutrophils // Cell Moll. Immunol., 2005. – Vol. 2(6). – P. 455-460.

19. Nanua S., Zick S.M., Andrade J.E. et al. Quercetin blocks airway epithelial cell chemokine expression // Am. J. Respir.Cell Mol.Biol., 2006. – Vol. 35(5). – P. 602-610.