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335. New insight into the pathophysiology of asthma

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Arterial stiffening in asthma exacerbation is connected with systemic inflammation, oxidative disbalance, hypoxemia and nitric oxide plasma level
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Arterial stiffness is an independent factor of cardiovascular risk. Exacerbation of asthma associates with increase arterial stiffness. The mechanisms responsible of this association are not clear.

Methods: We examined 54 patients with exacerbation of severe and moderate asthma and 25 age- and sex-matched healthy volunteers. Arterial stiffness was estimated by noninvasive arteriography (arteriograph TensioClinic TL1 (TensioMed, Hungary)). Plasma IL-10 and TNF- α levels were determined by the immune-enzyme analysis. Inflammation index calculated as ratio TNF- α / IL-10. Systemic oxidative disbalance was estimated by ratio of oxidative and antioxidative plasma activity, assessed by spectrophotometry. Hypoxemia was assessed by digital pulseoximetry. NO $^+$ plasma level was determined by Greiss's method.

Results: Central arterial stiffness was higher in patients with exacerbation of asthma, than in healthy persons. It was expressed in increase aortic pulse wave velocity (aPWV) and augmentation index (IA). As assessed by correlation analysis both (aPWV and IA) was strongly correlated with hypoxemia ($r=-0.921$ and $r=-0.876$ ($p<0.01$)) and inflammation index ($r=0.902$ and $r=0.868$ ($p<0.01$)). Less strongly but clearly aPWV and IA correlated with NO $^+$ level ($r=-0.543$ and $r=-0.367$ ($p<0.01$)) and systemic oxidative disbalance ($r=0.611$ and $r=0.459$ ($p<0.01$)).

Conclusion: Our results suggests that hypoxemia, systemic inflammation, hyponitroxidemia and oxidative disbalance can be involved in raising arterial stiffness in asthma exacerbation. This question requires future researches.

P3298

Differences of systemic arteries mechanical properties during remission and exacerbation of asthma

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Coexistence of cardiovascular disorders and asthma is ambiguous question. On the one hand vascular disturbances are important part of asthma pathogenesis. On the other hand the absence of serious vascular damage in asthma was remarked many times ago.

Methods: We examined 54 patients with severe and moderate asthma by noninvasive arteriography (arteriograph TensioClinic TL1 (TensioMed, Hungary)) during remission and exacerbation of disease. Control group included 25 age- and sex-matched healthy volunteers.

Results: The aortal stiffness in asthma exacerbation was increased. It was expressed in increase of aortic pulse wave velocity (aPWV) and augmentation index (IA). APWV and IA in asthma remission essentially improved and have reached control level. Moreover, IA in patients with remission of severe asthma was lower, than in healthy ones ($p<0.01$) and in patients with remission of moderate asthma ($p<0.01$). So IA in severe asthma was $-54.3\pm 7.8\%$; in moderate asthma $-38.6\pm 6.7\%$ and in controls $-40.9\pm 7.1\%$. The negative correlation between IA, severity and duration of disease has been observed ($r=-0.36$ and $r=-0.44$ ($p<0.01$)).

Conclusion: Results of our investigation may be connected with developing adaptation in response to regular influences of aggressive factors on vessel walls during asthma exacerbations. Established things can occur only without any irreversible changes of arteries. Our observation can partially explain diminish of cardiovascular risk in patients without of asthma exacerbation.

P3299

Arterial stiffness in patients with asthma

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A vascular disturbances has a great importance in asthma pathogenesis. Research of mechanical properties of vessels, in particular of arterial stiffness has special interest for the estimation of cardiovascular system function. **It is not clear** whether increase arterial stiffness observes in patients with asthma.

Methods: We examined 54 patients with severe and moderate asthma by noninvasive arteriography (arteriograph TensioClinic TL1 (TensioMed, Hungary)). Control group included 25 age- and sex-matched healthy volunteers.

Results: The aortal stiffness in asthma exacerbation was significant more, than in healthy persons. It was expressed in increase of aortic pulse wave velocity (aPWV) and augmentation index (IA). APWV in patients with severe asthma a two fold surpassed aPWV in healthy persons and was $10.5\pm 1.3\text{m/s}$. IA in such patients a 6 fold surpassed control level and was $14.4\pm 5.8\%$. Significant raised ($p<0.001$) arterial stiffness can take part in increasing cardiovascular risk during asthma

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exacerbation. Independently of increasing arterial stiffness in asthma exacerbation, aPWV and IA essentially improved and came nearer to control level in asthma remission. That suggests functional character of these changes. Augmented arterial stiffness in asthma correlates to lung ventilation dysfunction and hypoxia, disease duration and severity.

Conclusion: Described changes can explain cardiovascular events rising in patients with exacerbation of asthma. Our data suggests transitory character of arterial stiffness increasing in asthma exacerbation.

P3300

Identification of left ventricular systolic dysfunction or pulmonary hypertension in patients with asthma or chronic obstructive pulmonary disease by N-terminal pro-brain natriuretic peptide

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This study investigated the usefulness of NT-proBNP in recognising left ventricular systolic dysfunction or pulmonary hypertension in 480 outpatients with asthma or COPD.

Left ventricular function was impaired in 20 patients (4.2%) as evaluated by Doppler echocardiography. ProBNP levels were higher in patients with left ventricular dysfunction than in patients with normal function (median 1194 pg/ml vs 69 pg/ml, $p < 0.0001$). ProBNP cut-off values of 93 pg/ml for men and 144 pg/ml for women excluded left ventricular dysfunction with a negative predictive value of 99.7%. The sensitivity and the specificity were 95.0% and 68.0%, respectively. The positive predictive value was only 11% but many patients with elevated proBNP levels and normal left ventricular function had other significant cardiac abnormalities. 36 patients had systolic pulmonary artery pressures above 35 mmHg. ProBNP recognised an elevated pulmonary artery pressure with a sensitivity of 79.4% and a specificity of 68.6%. The positive and negative predictive values were 16.3% and 97.7%, respectively.

ProBNP appears to be an almost perfect test to rule out concomitant left ventricular systolic dysfunction or pulmonary hypertension in patients with obstructive lung disease. In the absence of left ventricular dysfunction, elevated proBNP levels are frequently seen in patients with left ventricular hypertrophy. Therefore, patients with obstructive lung disease and elevated proBNP should be referred for cardiologic evaluation thus enabling an early identification and treatment of this precursor of heart failure.

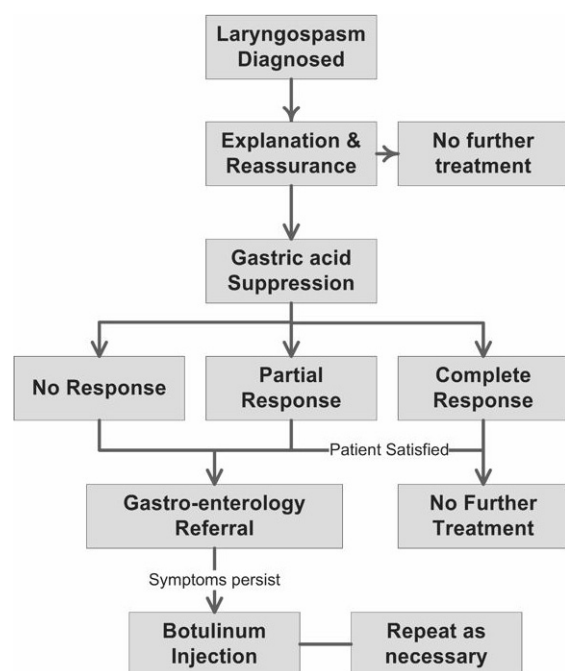
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An approach to the management of paroxysmal laryngospasm

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Background: To review the presentation, risk factors and management of paroxysmal laryngospasm.

Methods: All patients diagnosed with laryngospasm over a two-year period in a teaching hospital otolaryngology department with a subspecialty interest in airway disorders were reviewed. Information was obtained about disease presentation, risk factors, management and symptom resolution.



Results: Laryngospasm was diagnosed in nine women and six men. The average age at presentation was 56±6.5 years, and there was an 80 per cent association with gastro-oesophageal reflux disease. Proton pump inhibitors led to complete symptom resolution in six patients and to partial symptomatic relief, requiring no further treatment, in a further four patients. Of the remaining five patients unresponsive to PPI therapy, two continued to experience syncopal episodes due to laryngospasm. Both these patients achieved complete remission after laryngeal botulinum toxin injection. Symptoms recurred after three to four months and were successfully treated with a repeat injection.

Conclusions: The primary risk factor for spontaneous laryngospasm is laryngopharyngeal reflux. Symptoms are distressing and may be relieved in most cases by treatment aimed at suppressing gastric acid secretion. Laryngeal botulinum toxin injection appears to be a viable treatment modality in selected patients with refractory symptoms.

P3302

Implementation of NO measurement in the daily practice leads to more confident asthma diagnosis and has important effects on anti-inflammatory treatment

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Introduction: Nitric oxide (NO) in exhaled air can be used for the diagnosis and guidance of treatment of asthma in addition to conventional techniques, but how often NO changes the diagnosis or treatment is uncertain. In this prospective study 2 groups of patients were studied: 1. in patients referred with possible asthma we have added NO measurements to the usual techniques and evaluated whether the diagnosis and intended medication was changed. 2. In overt asthma patients we scored how often NO affected the anti-inflammatory treatment.

Results: Out of 160 patients 4 were not able to perform the procedure. Mean time spent with the NO procedure was 4.6 minutes.

Group 1: In all 73 patients spirometry was performed with PC20 or reversibility test. NO changed the diagnosis in 20 of these patients, in all cases the clinician was not completely sure of the diagnosis. In most of these patients the lung function was just positive for asthma. NO levels or altered diagnosis resulted in a change in medication in 23 patients.

Group 2: In 87 asthma patients the medication was at first intensified in 43% and diminished in 7% patients. With NO this was 33% and 15% respectively and thus often reduced ICS dosis.

There was no significant correlation between symptom score, spirometry and NO levels, indicating that these are independent parameters

Conclusion: NO measurement takes little time and can be performed in almost all patients. It changes the diagnosis especially in patients with uncertain diagnosis after the routine procedure. It facilitates titration of ICS in patients with asthma and affects the prescription in approximately 1/3 of the cases.

P3303

The relationship of lung diffusion capacity with airway obstruction in asthma

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The carbon monoxide diffusion capacity (DLco) measurement is an important pulmonary function test, giving information about gas exchange through the alveolocapillary membrane. In this study, the relationship between DLco and the degree of bronchial obstruction in patients with asthma has been investigated.

The study included 91 nonsmoker subjects (mean age: 37.2±9.4, range: 18–56 years) who were previously diagnosed as asthma and not having any diseases affecting DLco, and 47 nonsmoker voluntary subjects (mean age: 38.0±8.7, range: 22–56 years) as controls. Flow rates, lung volumes and DLco measurements of all subjects were performed via Vmax22 spirometry. High resolution computed tomography of all subjects were taken.

The patients were subdivided into 3 groups according to the degree of bronchial obstruction, using the parameters of FEV₁ and PEF defined in Global Initiative for Asthma (GINA) guideline. Patients who had FEV₁ and PEF values ≥ 80% were included into group 1 (n:25); FEV₁ or PEF values ≥ 80% and any one of FEV₁ or PEF values between 60 and 80% into group 2 (n:29); and any one of FEV₁ or PEF values ≤ 60% into group 3 (n:37).

There was not a statistically significant difference between patients with asthma and controls regarding to DLco, DLco (%pred), VA and DLco/VA values ($p > 0.05$). No statistical difference for the same parameters was noted among groups defined by the degree of bronchial obstruction, as well ($p > 0.05$).

DLco is not affected by the degree of bronchial obstruction in asthma. This is related to that the effective alveolar volume is not reduced in asthma. DLco measurement has an important role in differentiation of asthma, especially from emphysema.

P3304

Influence of combined antiasthmatic basic therapy on hyperinflation in patients with severe bronchial asthma

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The aim of our study was to compare influence of different schemes of basic treatment on hyperinflation in severe asthma patients

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Materials and Methods: 30 severe asthma patients ($FEV_1 < 50\%$), male – 12, female – 18, in the age 37 – 75 years, poorly controlled with common doses of inhalative steroids according their severity after 2 weeks run-in period (daily doses 500 mcg of fluticasone) were randomised 1:1 to receive (fluticasone 250 mcg + salmeterol 50 mcg) – (FP+SABA) BID + tiotropium bromide 18 mcg OD (I group), or (FP+SABA) (II group) during 2 months period. Data of bodyplethysmography and spirometry (MasterLab, Erich Jaeger) were studied before the and after 2 months of treatment.

Results: in I group significant ($p < 0.05$) decrease of RV – from (159.0 ± 4.9) to $(129.8 \pm 3.6)\%$, ITGV – from (131.5 ± 5.0) to $(106.9 \pm 4.1)\%$ was observed. Significantly in I group ($p < 0.05$) increased IC to 44.2 % and was noted more expressed tendency to the improvement of Rtot. Significantly ($p < 0.01$) improved in I group FEV_1 – from (42.4 ± 4.1) to $(59.3 \pm 4.8)\%$, FEF_{50} from (19.5 ± 2.5) till $(37.5 \pm 5.4)\%$, FEF_{25} – from (21.5 ± 2.0) till $(36.2 \pm 4.1)\%$. $FEF_{75-85\%}$ also had a tendency to the improvement.

In II group there was poor dynamics of the main functional indices: Rtot, TLC, VC kept on the primary level, to some degree decreased RV, there was a little trend for improvement in FEV_1 and MMEF.

Conclusions: addition of prolonged cholinolytic to basic therapy promoted the reduction of lung hyperinflation – significant increase of IC, decrease of RV, ITGV and tendency to normalization of Rtot, accompanied with positive dynamics of parameters of bronchial permeability.

P3305

Forced oscillation technique in patients with asthma

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Introduction: The forced oscillation technique (FOT) does not require considerable patient cooperation compared to spirometric test.

Aim: of our study was to assess whether the measurement of reactance and resistance by FOT technique can be used for assessment of asthma severity.

Method: A group of 33 patients with asthma was analyzed. Patients were divided in three groups following the criteria Global Initiative for Asthma (GINA). Pulmonary function was measured using spirometry and impulse oscillometry.

Results: Our results showed on table 1 and 2.

Conclusion: We concluded that FOT parameters significantly differed between the group of patients with severe persistent asthma and other two groups. Measurement of these parameters can be used for assessment of asthma severity, particularly in patients with severe persistent asthma who can't do correct spirometry due to uncooperation or severity of disease.

Table 1.

Severity of asthma	N	FEV1%	R5%	R20%	X5%	$\Delta X5$ (X5-X5ref)	Fres
Mild	9	84.2±16.32	123.22±40.4	119.55±32.78	185±140	0.09±0.03	14.42±5.62
Severe	8	54.4±15.26	262.63±86.8	190.00±54.04	1100±680	0.44±0.19	29.28±5.58
p		0.002	0.000	0.006	0.000	0.000	0.000

Table 2.

Severity of asthma	N	FEV1%	R5%	R20%	X5%	$\Delta X5$ (X5-X5ref)	Fres
Moderate	16	69.20±12.31	179.12±71.2	148.56±42.85	870±520	0.21±0.12	22.08±6.10
Severe	8	54.4±15.26	262.63±86.8	190.00±54.04	1100±680	0.44±0.19	29.28±5.58
P		0.03	0.009	0.061	0.040	0.000	0.008

P3306

Impulse oscillometry in evaluation therapy with combination fluticasone propionate and salmeterol in asthma patients

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Background: Impulse oscillometry (IOS, Jaeger, Germany) is more sensitive than spirometry, detecting early changes in small airways disease and in detecting responses to therapeutic and bronchial challenge.

Aim: Study was determined IOS in evaluation continuous therapy with combination fluticasone propionate and salmeterol (FSC), over a 12-month treatment and it was compared with results of spirometry, plethysmography, Asthma control test (ACT) and five point scale.

Method: Study was prospective, in 41 out-patients (24M: 17F), aged 10–65 with diagnosis of asthma and symptoms on previous ICS therapy. Patients visited hospital before therapy with FSC (Seretide Discus) and after 1, 6, and 12 months of treatment. The IOS measurements, spirometry, plethysmography, ACT and five point scale were performed.

Results: The average age was 33.8 years and 58.5% were man. Before therapy baseline values of IOS were, Z5: $218.4 \pm 87.9\%$ pred, R5: 208.7 ± 85.4 , R20: $164.0 \pm 91.7\%$ pred, X5: -0.25 ± 0.01 , and after one month were significantly changed ($p < 0.0001$), Z5: $176.1 \pm 76.6\%$ pred, R5: $167.0 \pm 69.0\%$ pred, R20: $148.9 \pm 71.4\%$ pred, X5: -0.16 ± 0.01 . Values of IOS, spirometry and plethysmography, ACT scores and five point scale scores were not performed significantly differences after 6 and 12 month. Correlation was significantly between R5 and FEV_1 (0.54), SRtot (0.59), and between X5 and FEV_1 (0.65), SRtot (0.68)

Conclusion: The IOS could be considered as like valid method for detecting lung function changes in evaluation therapy with the FSC.

P3307

Predictors of asthma progressive course in patients with autoimmune thyroiditis

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36 asthmatics with autoimmune thyroiditis (AIT) were included in trial. Patients were divided into three groups depending on the character of asthma course during 3–6 years: progressive course (A), stable moderate course (B), mild asthma or asthma's improving to mild (C). Patients with progressive course had significantly latest onset of asthma (45.7 ± 2.6 years) and AIT (52.2 ± 2.1 years) in comparison with group B (respectively 32.8 ± 2.7 ; $p < 0.005$ and 39.5 ± 3.7 ; $p < 0.005$) and group C (32.0 ± 4.4 ; $p < 0.001$ and 27.8 ± 4.4 ; $p < 0.001$). The FEV_1 was least in group A ($59.5 \pm 5.4\%$) in comparison with group B (79.0 ± 5.5 ; $p < 0.005$) and group C (100.9 ± 5.9 ; $p < 0.001$). Spirometry results in patients with $FEV_1 < 70\%$ revealed increase of airways obstruction's reversibility in hypothyroid asthmatics ($49.6 \pm 6.3\%$) in comparison with eu- ($29.3 \pm 6.4\%$; $p = 0.03$) and hyperthyroid ($20.5 \pm 11.8\%$; $p = 0.06$) patients. The concomitant diseases frequency was largest in patients of group A (IHD, hypertension: 92.3%, $p < 0.01$; COPD: 69.2%, $p < 0.05$). In these patients correction of hypothyroidism and treatment by β -agonists were most difficult due to cardiac pathology. There weren't significant differences in doses of inhaled steroids between group A, B and C. These data explain more severe asthma course in hypothyroid patients with moderate and severe asthma including because of increase of bronchoconstriction's degree and difficulty of correction of hypothyroidism. Also 73% of woman of group A mentioned worsening of asthma course during menopause. Thus predictors of asthma's progressive course in patients with AIT are late onset of asthma and AIT, multiple concomitant diseases, menopause (for woman) and hypothyroidism (for asthmatics with $FEV_1 < 70\%$).

P3308

Eosinophilic pneumonias (EP) among patients with peripheral blood eosinophilia in the material of allergology clinic

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In clinical practice peripheral blood eosinophilia (PBE) is widely used as a marker of allergic diseases, but it may reflect not only allergic stimulation of eosinophil proliferation. PBE and/or eosinophil prominent infiltration of the lung parenchyma are characteristic features of eosinophilic pneumonias (EP). PBE might be also present in other bronchopulmonary disorders where EP is not prominent.

Aim: Assessment of the incidence and clinical analysis of EP cases among patients with PBE.

Material and Methods: Sixty four patients with PBE ($> 0.5 \times 10^9$ eosinophils/l) diagnosed in our Department in the years 2003–2005 were analyzed. Wide diagnostic process was performed in each case to establish a possible cause of hypereosinophilia.

Results: In 7 (11%) patients with PBE (mean count of eosinophilia 2.86×10^9 eosinophils/l; $SD \pm 2.67$), EP was diagnosed, including Churg-Strauss syndrome ($N = 3$), hypereosinophilic syndrome ($N = 1$) and allergic bronchopulmonary aspergillosis ($N = 3$). Miscellaneous group of lung diseases with some degree of eosinophilia (on average 0.88×10^9 eosinophils/l; $SD \pm 0.41$) consisted of 47 (73%) subjects including patients with asthma ($N = 31$), COPD ($N = 10$), pulmonary sarcoidosis ($N = 3$), allergic extrinsic alveolitis ($N = 2$), and Pneumocystis pneumonia ($N = 1$). PBE was significantly higher in EP patients than in patients with miscellaneous bronchopulmonary diseases ($p < 0.0001$).

Conclusions: EP is not frequent cause of PBE in clinical practice. In wide spectrum of bronchopulmonary diseases with possible PBE, EP is characterized by prominent blood eosinophil counts.

P3309

HLA and DR in patients with asthma and atopy in Macedonia

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Structures bearing MHC antigens play a major role in immunity and self-recognition of cells and tissues. Numerous articles refer to the association of HLA and DR antigens to the expression of atopy to certain allergens and bronchial asthma (BA), as well as their heredity.

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We evaluated 160 asthmatic patients, in order to estimate the distribution of HLA antigens class I (*A,B* and *C*) and class II (*DR*) in BA, as well as their connection to the incidence of atopy (standard prick testing) and the family history of atopy. 103 of them had atopic (positive prick test to dermatophagoides pt-48, pollen-18, grass pollen-15, and DP+pollen-22), and 57 had nonatopic BA; 91 had positive and 69 negative family history of atopy or BA.

We found highest incidence of *A1,A2,A3,B5,B7,Cw3*, *HLA Ag*, *DR2,DR3* and *DR7*, compared to *A1,A2,A9,B5,B12*, *B35* (study of 1300 healthy volunteers in Macedonia, Kolevski 1988). In the patients with positive atopy we found statistically significant association with *HLA A9*, *B5* and *DR 3*, in those with positive family history we had significantly higher incidence of *A9,A10* and *B5*, while cumulatively in all of the patients we found significant association of the BA with *A3,A9,B5* and *Drw52*.

P3310**Plasma leptin in asthma patients with steroid induced diabetes compared with obesity patients**

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Leptin is a hormone of adipose tissue and skeletal muscle. Dosis increase of exogene leptin induces decrease of circulated insulin level in ob/ob mice. In db/db mice this decrease does not take place because of insulin resistance. The aim of our study was to compare leptin levels of asthma patients complicated by steroid induced diabetes (group 1) with obesity patients (group 2). Group 1 included 21 patients – 10 males and 11 females with mean age 54.5/males and 58.8/females and BMI 32.23 kg/m² and 33.85 kg/m² respectively. Group 2 included 12 patients – 7 males and 5 females with mean age of 59.6 and 57.4 and BMI 32.32 kg/m² and 32.23 kg/m² in males and females respectively. Leptin plasma was measured by specific ELISA kit. Blood samples were obtained fasting. Normal range for leptin values was 3.63–11.09 ng/ml/females and 2.05–5.67 ng/ml/males. Student t-criterium was used to determine the significance of differences. We found in asthma patients with normal BMI leptin levels of: 1.99 ng/ml/males and 11.01 ng/ml/females. Asthma patients with increased BMI had 9.16 ng/ml and 23.56 ng/ml appropriately. In group 2 it was 13.86 ng/ml/males and 22.55 ng/ml/females. We suppose that asthma patients with increased BMI and obesity patients have disorder in nutrition behaviour because of the disorder of leptin function as a result of disorder in receptor functioning. These patients can be in theory compared to db/db mice. Asthma patients with normal BMI can be in theory compared with mice, that have mutations in the leptin gene (ob/ob mice). Treatment with exogene leptin could allow us to decrease dosis of oral antidiabetic drugs and normalise glucose levels in our patients.