Uncontrolled asthma determinants in overweight and obese adults

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Abstract: Relevance of the research — epidemiological and clinical studies in recent years confirmed the existence of a bronchial asthma (BA) phenotype associated with obesity. In the current literature, obesity is considered a possible risk factor for the development of BA. Nonetheless, the factors contributing to the uncontrolled course of BA among overweight patients need to be elucidated. The need for a personalized approach to patient management is reflected in the latest edition of the international consensus document on the asthma treatment – GINA (Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention). Despite substantial number of epidemiological studies on the prevalence of BA in obese patients, the threshold values of major risk factors for the development of uncontrolled BA (vitamin D, IL-17, IL-10, BMI; intake of total fat, carbohydrates and cholesterol) remain unclear. Objective: to identify the risk of developing an uncontrolled course of BA depending on the levels of IL-17, IL-10 and vitamin D; dietary characteristics (intake of total fat, cholesterol and carbohydrates); and body mass index (BMI).

Material and methods — The study involved 79 patients with an established diagnosis of BA, 18-69 years old. Patients were split among three groups according to their BMI values. Group I included 27 patients with normal body weight (BMI: 18.5-24.9 kg/m²), 56 (42-61) years of age. Group II comprised 28 overweight patients (BMI: 25-30 kg/m²), 57 (50.5-63.5) years of age; Group III encompassed 24 obese patients (BMI≥30 kg/m²), 58 (54-65) years of age.

Results — the risk of developing uncontrolled BA increased by 1.8 times with increase of a total fat intake (95% CI: 1.28-2.72; p=0.001); by 5.7 times with BMI≥26.7 kg/m² (95% CI:2.05-15.92; p<0.001); by 5.2 times with IL-17 level >83.5 pg/mL (95% CI:1.71-15.8; p=0.003); by 8.32 times with vitamin D content <24.5 ng/mL (95% CI: 2.9-23.72; p<0.001).

Conclusion — patients with BMI≥26.7 kg/m², vitamin D deficiency (i.e., vitamin D content <24.5 ng/mL), IL-17 content >83.5 pg/mL, as well as excessive consumption of total fat, carbohydrates and cholesterol, could be attributed to the risk group for developing an uncontrolled BA.

Keywords: bronchial asthma, body mass index, BMI, vitamin D, obesity, actual nutrient intake.

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A number of authors confirmed the effect of vitamin D on humoral and cellular immunity in vitro experiments [13]. However, none of the studies has conducted a comprehensive assessment of the individual actual nutrient intake in BA patients, in conjunction with a biochemical study of the levels of vitamin D, IL-10, and IL-17 in the blood serum.

A large number of BA patients have a stereotypical idea of the need to follow a hypoallergenic diet, consequently restraining from the intake of a number of products. Fruits and vegetables are often excluded, which can lead to a higher intake of simple carbohydrates and fats in the diet [14].

Research objective: to determine the risk of developing uncontrolled BA, depending on the levels of IL-10, IL-17, vitamin D, dietary characteristics (total fat, carbohydrates, cholesterol), and body mass index (BMI).

Material and Methods

Research design

The study involved 79 patients with an established diagnosis of BA. Their median age was 57 (50-63) years. Of these, 22 (27.8%) were men and 57 (72.2%) were women. The study groups were dominated by patients with BA phenotype (χ2=10.97, p=0.005). We compared the BA severity stages (mild, moderate, or severe), the phenotype, and the degree of control were evaluated, based on the criteria of the Global Asthma Initiative 2019 (GINA).

All patients underwent the ACT. The sum of points on the questionnaire fewer than 20 was considered an uncontrolled course of BA, whereas more than 20 was interpreted as the controlled BA course.

To evaluate the structure of patients’ nutrition, a survey-weight method was used. All participants kept food diaries for 21 days in a row, on the basis of which, the daily diet was subsequently analyzed. Prior to the study, all respondents received a standardized form to fill out, and were given detailed instructions on keeping their food diary, as well as on weighing foods and dishes. The diary provided detailed information on all daily meals and snacks, and reflected the following indicators: the time of the meal, the name of the dish or food item, the weight of the serving, the composition of the dish, the weight of the dish components. Additional notes indicated the macronutrient composition and calorific value of the consumed foods.

The caloric values and chemical composition of the food products were calculated on the basis of the data provided by VA Tutyelyan in his Handbook of Dietetics (2002) [15]. The evaluation of the obtained results was carried out in accordance with the requirements of the Guidelines 2.3.1.2432-08 ‘Norms of Physiological Needs in Energy and Nutrients for Various Groups of the Russian Federation Population’.

The ELISA technique was used to study the content of IL-17, IL-10, and the level of vitamin D in the blood serum. The determination of the serum IL-10 and IL-17 content was carried out using commercial kits for conducting solid-phase enzyme immunoassay (TIFA) of the Cytokine company (Russia), in accordance with the manufacturer’s instructions. The study was carried out on the automatic analyzer, Multiskan™, Thermo Fisher Scientific (USA). Identification of vitamin 25(OH)D (25-hydroxycholecalciferol) content in the blood serum was performed using commercial ELISA kits from BioChemMak, JSC (Russia), manufactured by DIAsource ImmunoAssays (Belgium). In vitamin 25(OH)D ELISA kits, a sandwich version of TIFA was used.

Table 1. Characteristics of the examined patient groups

| Parameters                                      | Normal BMI (Group I) n=27 | Overweight adults (Group II) n=28 | Obese adults (Group III) n=24 | Statistical significance |
|-------------------------------------------------|---------------------------|-----------------------------------|-------------------------------|--------------------------|
| Age, years                                      | 56 (42-61)                | 57 (50.5-63.5)                    | 58 (54-65)                    | p>0.05                   |
| Men, number (%)                                 | 8 (29.6%)                 | 9 (32.1 %)                        | 5 (20.8 %)                    | χ² = 0.887 p>0.62        |
| Women, number (%)                               | 19 (70.4 %)               | 19 (67.9 %)                       | 19 (79.2 %)                   |                          |
| ACT, points                                     | 25 (23-25)*               | 23 (17-25)                        | 15 (10-23)                    | p>0.05                   |
| FEV1 (%)                                        | 2.32 (1.91-2.68)*         | 2.09 (1.88-2.67)                  | 1.81 (1.39-2.31)              | p>0.05                   |
| BA with the late onset, number (%)              | 22 (83.5 %)               | 19 (67.9 %)                       | 9 (37.5 %)                    | χ² = 10.9 p<0.05         |
| FEV1 (%)                                        | 96 (87-108)*              | 94 (84.5-102.5)                   | 80.5 (63-94.5)                |                          |
| Allergic asthma phenotype, number (%)          | 5 (18.5%)                 | 9 (32.1 %)                        | 15 (62.5%)                    |                          |

* Comparative analysis of the values (Group I vs. Group III). BMI, body mass index; ACT, asthma control test; FEV1, the forced expiratory volume in the first second; BA, bronchial asthma.
Before the study, all participants signed a written consent to participate. Depending on how well the data matched normal distribution, the following calculated indicators were used to describe the quantitative data: Me (IQR), where Me is the median, and IQR is an interquartile range between the values of 25th and 75th percentiles. As for statistical analysis, the methods of descriptive statistics and the method of identifying the statistical significance of differences (the Mann-Whitney U test) were employed. The comparison quantitative among three independent groups with distributions different from the normal distribution was performed using the Kruskal-Wallis test. The comparisons of discrete variables among different groups was carried out using the standard method of analyzing the contingency tables (χ² sensu Pearson).

Logistic regression was used to determine the nonlinear relationships of binary variables with qualitative and/or quantitative parameters. The odds ratio (OR), i.e., an occurrence of an adverse event, and the 95% confidence interval (CI) were calculated.

To assess the effects of body weight and vitamin D on the course of BA, the ROC curve analysis (Receiver Operating Characteristic) was used. To obtain a numerical value of the effect of obesity on the course of BA, we estimated the Area Under the Curve (AUC).

The obtained results were processed using the Statistica v.10 program, and the differences were considered statistically significant at p<0.05.

Results

Physical and instrumental examination of patients with a normal body weight revealed statistically significantly lighter course of BA, compared with overweight and obese patients (χ²=10.9, p<0.05) (Table 2).

All patients received basic anti-inflammatory therapy with inhaled glucocorticosteroids (IGCS), depending on the BA stage. Baseline therapy was evaluated in accordance with low, medium and high doses of IGCS according to the International Consensus. The majority of patients received IGCS in medium doses [43 (54.4%) patients]; high doses were used by 11 (13.9%) and low doses were used by 25 (31.7%) patients.

Based on anamnesis and ACT data, controlled BA was established in 22 (45.8%) patients with normal BMI, 17 (35.1%) overweight patients, and 9 (18.75 %) obese subjects. Uncontrolled BA was detected in 5 (16.1%) patients with normal BMI, 11 (35.5%) overweight patients, and 15 (48.8%) obese participants (Table 3).

According to the study, the energy value of the daily diet exceeded the upper limit of the energy requirement for obese and overweight patients. E.g., in Group II, the daily energy consumption was 2520.9 (2250.8-2765.8) Kcal/day, whereas the upper limit of energy demand was just 2096.5 (1845.5-2322) Kcal/day (U=169, Z=3.65, p<0.001). In Group III, these numbers were 3522.7 (2970-4398) Kcal and 2290 (2168-2500) Kcal, respectively (U=24, Z=5.43, p<0.001).

The analysis of the actual nutrient intake showed an unbalanced diet in all studied groups of patients. Accordingly, in Groups I and II, an excess of carbohydrates’ intake was detected (79% and 80.7%, respectively, of the total caloric content of consumed food). In Group III, there was an increase in the intake of total fat from food, including at the expense of saturated fatty acids (SFA) (41.4%).

The diet of patients with uncontrolled BA was characterized by a higher intake of total fat, SFA, cholesterol, and carbohydrates, compared with the diet in subjects with controlled BA. Hence, the total fat consumption among these patients was 161.0 (101.3-218.9) g/day, protein intake was 96.0 (79.3-117.7) g/day; SFA were consumed in the amount of 45.6 (31.2-69.6) g/day and total carbohydrates’ intake was 439.9 (326.9-570.1) g/day (Table 4).

In a one-dimensional logistic model of the BA course, the predictors for the development of an uncontrolled BA course included an increase in the consumption of total fat (including SFA), cholesterol, and total carbohydrates; along with an increase in the caloric value of consumed food (Table 5).

In the multivariate logistic model of BA, the only predictor of uncontrolled BA development was associated with the level of total fat consumption.

Table 2. Stages of bronchial asthma severity versus BMI

| BA severity stages | Groups | n=27 | Groups | n=28 | Groups | n=24 |
|--------------------|--------|------|--------|------|--------|------|
| Mild BA            |        |      |        |      |        |      |
| n=13               |        |      | n=13   |      | n=21   |      |
| (48.2%)            |        |      | (48.2%)|      | (87.9%)|      |
| 14 (25.9%)         |        |      | 6 (21.4%)|      | 7 (28.3%)|      |
| 2 (8.3%)           |        |      |        |      |        |      |
| Moderate BA        |        |      |        |      |        |      |
| n=12               |        |      | n=18   |      | n=17   |      |
| (44.4%)            |        |      | (64.2%)|      | (70.8%)|      |
| 17 (70.8%)         |        |      | 14 (77.8%)|      | 10 (58.8%)|      |
| 5 (20.8%)          |        |      |        |      |        |      |
| Severe BA          |        |      |        |      |        |      |
| n=2                |        |      | n=3    |      | n=5    |      |
| (7.4%)             |        |      | (10.7%)|      | (20.8%)|      |
| 3 (15.8%)          |        |      | 4 (26.6%)|      | 3 (60.0%)|      |
| χ²=10.9; p<0.05.   |        |      |        |      |        |      |

| Table 3. Asthma control versus BMI |
|-----------------------------------|
| BMI-based groups                  | Controlled BA (100 %) | Uncontrolled BA (100 %) |
| Group I n=27                     | 22 (45.8%)            | 5 (16.1 %)              |
| Group II n=28                    | 17 (35.4%)            | 11 (35.5 %)             |
| Group III n=24                   | 9 (18.8 %)            | 15 (48.4 %)             |
| χ²=10.31; p<0.05.                | BMI, body mass index. |

| Table 4. Consumption of essential nutrients by patients with asthma |
|-------------------------------------------------|
| Parameters                                      | Controlled BA | Uncontrolled BA |
| Parameters                                      | Me (IQR)      | Me (IQR)       | U  | p     |
| Total fat, g/d                                 | 89.1 (61.7-130.3) | 161.0 (101.3-218.9) | 399.0 | 0.001 |
| SFA, mg/d                                       | 35.9 (25.6-45.6) | 45.6 (31.2-69.6) | 450 | 0.003 |
| Cholesterol, mg/d                              | 223.8 (154.2-280.8) | 294.8 (183.2-418) | 507 | 0.02 |
| Proteins, g/d                                  | 67.5 (56.6-88.0) | 96.0 (79.3-117.7) | 376.0 | <0.001 |
| Common carbohydrates, g/d                      | 300.5 (223.6-408.4) | 439.9 (326.9-570.1) | 413.0 | 0.001 |
| SFA, saturated fatty acids; Me, median; IQR, interquartile range. |
In order to determine the probability of developing an uncontrolled course of BA against the background of excess body weight, we conducted the ROC analysis. The AUC for BMI was 0.26 (95% CI: 0.15-0.377; p<0.001). The threshold value for BMI was 26.7 kg/m² (sensitivity: 64%; specificity: 77%). The odds ratio of developing uncontrolled BA at BMI >26.7 kg/m² was 5.7 (95% CI: 2.05-15.92; p<0.001) (Table 6). According to our results, it is arguable that the risk of developing uncontrolled BA is higher among overweight patients.

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Evaluation of IL-17 levels in patients with BA revealed statistically significant differences between Group I and Group III. When comparing Groups I and II, no statistically significant differences in the levels of IL-17 were detected (U=277, Z=1.18, p=0.09) (Table 7).

IL-17 content increased with an increase in BMI in the group with controlled BA (r=0.29, p<0.05). There was no statistically significant association between IL-10 and BMI.

In order to determine the probability of developing an uncontrolled course of BA with increase in IL-10 content, we performed the ROC analysis. The AUC for IL-10 was 0.29 (95% CI: 0.19-0.43; p<0.003). The threshold value for IL-10 was 83.5 pg/mL (sensitivity: 50%; specificity: 80%). The odds ratio for developing uncontrolled BA at IL-10 >83.5 pg/mL was 5.2 (95% CI: 1.71-15.8; p=0.003) (Table 6).

Vitamin D levels were significantly dependent on BMI. The median vitamin D level was 31 (25.2-34.5) ng/mL for patients with normal BMI, 25.5 (18.2-28.9) ng/mL for overweight patients, and 18 (15.5-23.6) ng/mL for obese patients (Table 8).

| Parameters | OR (95% CI) | p   |
|------------|-------------|-----|
| Energy value | 1.04 (1.02–1.07) | 0.002 |
| Common fat  | 1.87 (1.28–2.72) | 0.001 |
| SFA         | 5.68 (1.68–19.24) | 0.005 |
| Common carbohydrates | 1.25 (1.08–1.44) | 0.003 |
| SFA, saturated fatty acids; OR, odds ratio; CI, confidence interval. |

Table 7. The effect of actual nutrient intake on the risk of uncontrolled bronchial asthma

| Parameters                        | OR (95% CI) | p   |
|-----------------------------------|-------------|-----|
| BMI>26.7 kg/m²                    | 5.7 (2.05-15.92) | p<0.001 |
| IL-17>83.5 pg/mL                  | 5.2 (1.71-15.8) | p=0.003 |
| Vitamin D>24.5 ng/mL              | 8.32 (2.9-23.72) | p<0.001 |
| OR, odds ratio; CI, confidence interval; BMI, body mass index. |

The AUC for vitamin D was 0.844 (95% CI: 0.760-0.928; p<0.001). Threshold value: 24.5 ng/mL (sensitivity: 77%; specificity: 70%). The ratio of the chances to develop an uncontrolled course of BA at the level of vitamin D >24.5 ng/mL was 8.32 (95% CI: 2.9-23.72, p<0.001) (Table 6).

Hence, overweight patients with vitamin D deficiency (vitamin D level <24.5 ng/mL) and IL-17 level >83.5 pg/mL could be attributed to the risk group for developing the uncontrolled BA.

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Discussion

The cause of the imbalance between the immunoregulatory subpopulations of T-lymphocytes, leading to the development of severe uncontrolled BA, remains debatable [16]. Currently, exogenous factors affecting the immune response formation began attracting greater attention. Among important risk factors for the development of uncontrolled BA, we should mention overweight status and obesity. A number of studies demonstrated that patients with BA against the background of obesity have a more severe course of the disease [17]. A progressive increase in BMI can lead to the formation of a specific BA phenotype. BA against the background of obesity is characterized mainly by neutrophil inflammation in the respiratory tract and an increase in IL-17 production [18, 19].

Our study showed a significant increase in the level of proinflammatory cytokine IL-17 in the group of patients with uncontrolled BA and overweight status, which could explain the more severe course of BA among obese patients. There were no statistically significant differences between the IL-10 level and BMI. The prospects for personalized therapy of BA are associated with identification of biomarkers, determining the uncontrolled BA course, in particular, with the level of IL-17.

In the course of analyzing the obtained data, we identified the threshold values of risk factors for uncontrolled BA (vitamin D level ≥24.5 ng/mL, IL-17 level >83.5 pg/mL, BMI >26.7 kg/m²). Based on our results, it is possible to identify the patients who are at risk of uncontrolled course of the disease.

The values of vitamin D and IL-17 levels could be attributed to drug-modified risk factors. Drug correction of vitamin D is a fairly easy task [22], which cannot be stated about the level of IL-17 [20, 21]. Changing eating behaviors is also a challenge for the patients. A number of authors suggested that patient education and explaining them the risks, associated with their overweight status, could increase their adherence to a balanced diet [23].

An important finding is that an increase in patients’ adherence to a healthy diet may contribute to improved treatment outcomes without changing the underlying therapy [24].
Table 8. Dependence of vitamin D levels on BMI

| Group                        | Statistical significance |
|------------------------------|--------------------------|
| Normal BMI / Overweight status | Z=4.24 p<0.001          |
| Normal BMI / Obesity         | Z=2.24 p<0.001          |
| Overweight status / Obesity  | Z=2.09 p=0.12          |

BMI, body mass index.

Conclusion

An increase in the energy value of the diet, excessive consumption of the total fat – including at the expense of SFA, cholesterol, and carbohydrates increases the risk of developing an uncontrolled course of BA. The risk of developing an uncontrolled course of BA in patients with a BMI over 26.7 kg/m² increases by 5.7 times (p<0.001).

Due to the significant impact of BMI and excessive consumption of the total fat, cholesterol and carbohydrates on disease the course, the analysis of the actual nutrient intake in patients is an important link in a personalized approach to the patient management.

A decrease in the content of vitamin D in the blood serum of less than 24.5 ng/mL increases the risk of developing an uncontrolled course of BA by 8 times (p<0.001). Hence, low level of vitamin D could be considered a predictor of the uncontrolled BA development.

The formation of T₄=17 immune response is more typical for overweight patients. The development of an uncontrolled course of BA in patients with IL-17 levels greater than 83.5 pg/mL increases by 5.2 times (p=0.003).

Ethical approval

All studies were conducted in compliance with the ethical standards of the Declaration of Helsinki and the European Union directives. All research activities were approved by the Ethics Committee of Samara State Medical University.

Conflict of interest

We declare that we have no conflicts of interest.

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