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Clinical features of asthma-COPD overlap syndrome with comorbid type 2 diabetes mellitus

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Abstract. ***Background.*** *Comorbidity profiles are a common subject of research in patients with asthma-COPD (chronic obstructive pulmonary disease) overlap (ACO), but in case of concurrent type 2 diabetes mellitus (T2DM), there is a lack of targeted research on the quality of life, clinical course, and lung function. The aim of the study was to clarify the clinical features of asthma-COPD overlap in combination with T2DM.* ***Materials and methods.*** *Sixty-nine patients were examined: 24 with ACO and T2DM (group 1), 21 with asthma and T2DM (group 2), and 24 with COPD and T2DM (group 3). A diagnosis of ACO was made according to GINA and GOLD 2017 guidelines. Quality of life was assessed using the CAT, ACQ, and SGRQ, and the severity of dyspnea was assessed using the mMRC scale, disease severity and prognosis using the BODE index. Spirometry with bronchodilation test, 6-minute walk test, and bioimpedance analysis were performed.* ***Results.*** *Patients in the main group had a higher total SGRQ score than those in group 3 (by 33 %, p = 0.001). Higher ACQ and total SGRQ scores indicate a trend toward worse asthma control and lower quality of life in patients with ACO and T2DM compared to the asthma + T2DM group (p = 0.056 and p = 0.054, respectively). Body mass index was higher than in patients with COPD and T2DM (by 16.3 %, p = 0.001). Higher serum glucose levels were found in patients with ACO and T2DM than in those with COPD and T2DM (by 18.3 %, p = 0.028). The FEV_1 in the ACO and T2DM group was lower than in the asthma + T2DM group (by 18.7 %, p = 0.027), and the SVC was lower by 33 % (p = 0.021). There was a tendency to a lower result in the 6-minute walk test in the main group compared to patients from group 3 (p = 0.0548), and a higher frequency of exacerbations per year compared to groups 2 (p = 0.08) and 3 (p = 0.06).* ***Conclusions.*** *Patients with asthma-COPD overlap and concurrent type 2 diabetes mellitus have worse quality of life, lower FEV_1 and SVC, submaximal exercise tolerance, higher fasting glucose levels, and a tendency towards increased exacerbation frequency.*

Keywords: *asthma; chronic obstructive pulmonary disease; asthma-COPD overlap; type 2 diabetes mellitus; comorbidity; quality of life; pulmonary function*

Introduction

According to the adapted GINA 2022 guideline, asthma-COPD (chronic obstructive pulmonary disease) overlap (ACO) is characterized by persistent airflow limitation with some features typical for asthma or COPD [1–3].

Due to the lack of clear diagnostic criteria for ACO and different patient cohorts from which they are identified, the prevalence of this combination varies widely depending on the criteria used [4, 5]. According to a systematic review conducted by GOLD 2021 involving over 36,700 patients in 20 countries, the prevalence of ACO was relatively low, ranging from 1.8–15.9 %, which was attributed to the inability to make accurate comparisons across countries due to the lack of a universally recognized definition [6]. A. Romem et al. [7], citing the joint recommendations of GINA and GOLD 2015, attribute the significant differences in the prevalence of ACO to the fact that studies often involve patients with established diagnoses of COPD or asthma rather than primary populations based on spirometry data or respiratory symptoms. A meta-analysis of population-based studies conducted in 2019 determined the global prevalence of ACO to be 2 % [8].

Comorbidity profiles are a common subject of research in patients with ACO, but in the case of concomitant type 2 diabetes mellitus (T2DM), there is a lack of targeted studies on quality of life, clinical course, and lung function [9–11]. In particular, L. Peltola et al. found that a higher number of comorbidities had a negative impact on the survival of patients with ACO as well as COPD. In this retrospective

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study, they also found better survival rates in ACO patients hospitalized with exacerbations, and they were more likely to be overweight than patients with COPD [11].

A study on the comorbidity profile in patients with COPD was conducted in Germany in 2020. Among the twenty most common comorbid conditions were lipid metabolism disorders (43 %), T2DM (27.8 %), and obesity (27 %) [12].

Reduced lung function in chronic lung diseases and the development of T2DM are bidirectional processes, because diabetes is among the comorbidities that are frequently found in patients with COPD and asthma, and their presence increases the risk of exacerbations [13–15] and mortality [16]. Moreover, in a 12-year study, it was found that each 1% decrease in forced expiratory volume in 1 second (FEV_1) was statistically significantly associated with a higher (2.5%) risk of diabetes, while each 1-liter increase in FEV_1 was associated with a 53% reduction in the risk [17].

Aim of the study: to investigate the features of the clinical course of asthma-COPD overlap with comorbid type 2 diabetes mellitus.

Materials and methods

Twenty-four patients with ACO and T2DM (group 1), 21 patients with asthma and T2DM (group 2), and 24 patients with COPD and T2DM (group 3) were examined. The average age of patients with ACO + T2DM was 60 years [52.75; 62.75], asthma + T2DM was 64 years [61; 65], and COPD + T2DM was 61.5 years [56.25; 75.25]. The study included 54 men (78.2 %) and 15 women (21.8 %). The smoking index (pack-years) for the groups was 8 [35], 10 [20], and 4 [20], respectively. The diagnosis of ACO was made according to the recommendations of GINA and GOLD 2017. Patients met the inclusion and exclusion criteria for the study and provided informed consent. To evaluate symptoms, their impact on the patient's life with COPD, and to determine possible risks, the COPD assessment test (CAT), Asthma Control Questionnaire (ACQ), and St. George's Respiratory Questionnaire (SGRQ) were used. The degree of dyspnea was assessed using the mMRC scale. The BODE index was used to assess the severity of the disease course and prognosis. Lung function and bronchodilator test with a short-acting β2-agonist (salbutamol 400 mcg) were evaluated using the BTL 08 SpiroPRO spirometer (UK). Patient tolerance to physical activity was measured using a 6-minute walking test. Bioimpedance analysis was performed using the portable Tanita BC-601 device (Japan). The BMI, percentage of body fat, trunk fat, and muscle mass (kg) were evaluated. The fasting glucose level was determined by the glucose oxidase method, glycated hemoglobin (HbA1c) by the photocolorimetric method, insulin by the enzyme-linked immunosorbent assay, and the HOMA-IR index was calculated using the formula: glucose (mmol/L) × insulin (μU/mL) / 22.5.

The obtained results were statistically processed using the software package Statistica 10.0 by StatSoft Inc. Non-parametric criteria were used for independent samples, including the Kruskal-Wallis multiple comparisons test (2-tailed p-values) and the Mann-Whitney U Test. The indicators are expressed as a median [interquartile range] (Me [IQR]). A statistically significant difference between the values of the indicators was considered to be present if $p < 0.05$.

Results

In patients with a comorbid course of ACO and T2DM, the frequency of exacerbations per year was slightly higher than in patients in the second and third groups, respectively (Table 1), but there was no statistically significant difference ($p_1 = 0.08$, $p_3 = 0.06$).

According to the CAT questionnaire, patients with ACO and T2DM had the same strong impact on their quality of life as patients with COPD + T2DM, and no statistically significant difference was found between the groups ($p > 0.05$). The results of the ACQ questionnaire and the higher total score of the SGRQ indicate a trend towards worse asthma control and lower quality of life in patients with ACO and T2DM compared to the asthma + T2DM group ($p = 0.056$ and $p = 0.054$, respectively).

When analyzing the data from the SGRQ, patients in the first group had a higher total rating of the impact of the disease on their general health status by 33 % ($p = 0.001$) and 55.5 % ($p < 0.001$) on the symptom scale compared to the third group of patients, as well as 38.5 % ($p = 0.042$) on the activity scale compared to the second group of patients. On the scale measuring the impact of the disease on psychosocial breathing-related problems in patients with ACO and T2DM, there was a higher number of points by 44.7 % ($p = 0.04$) and 34.1 % ($p = 0.039$) compared to the other two groups. The mMRC scale showed that dyspnea was the most severe in patients in the first group, with it being more frequently present at rest and during physical exertion. However, no statistically significant difference was found between patient groups ($p > 0.05$). The BODE index did not differ statistically between groups.

During the bioimpedance analysis, it was found that the BMI was higher by 16.3 % in patients with ACO and T2DM compared to those with COPD + T2DM ($p = 0.001$). The muscle mass content was also higher by 16.2 % ($p = 0.001$) in the first group compared to the third group. The percentage of body fat and trunk fat did not differ significantly between the groups.

Spirometry measurements showed that the FEV_1 in the ACO and T2DM group was 18.7 % lower with a statistically significant difference between the group and the asthma + T2DM group ($p = 0.027$).

Our study did not show a statistically significant difference between the groups for the FVC parameter, but there was a significant difference in SVC ($p = 0.021$) with 33 % lower values in the first group compared to the third group.

According to the results of the 6-minute walk test, the patients in all three groups covered a relatively similar distance, although there was a tendency towards lower results in the first group compared to patients in the third group ($p = 0.0548$).

Patients with ACO and T2DM had higher fasting glucose levels by 18.3 % compared to patients with COPD and T2DM ($p < 0.05$, $p = 0.028$). There was no statistically significant difference in HbA1c levels between the first group and patients with either asthma or COPD alone. Insulin levels in patients with asthma and T2DM were 36 % higher than in patients with COPD and T2DM ($p = 0.001$). The HOMA index and insulin levels in patients with ACO and T2DM were higher than in patients with COPD and T2DM, although there was no statistically significant difference.

Discussion

The study by Jeong U. Lim et al. [4] found that patients with ACO had worse quality of life according to CAT and SGRQ tests, as well as lower FEV_1 levels compared to a COPD cohort who did not meet ACO criteria. There was no statistically significant difference in the distance walked in 6 minutes in any of the criteria applied, except for the established diagnoses by specialists. It is worth noting that S. Peerboom et al. found worse control and lower quality of life, lower FEV_1, higher leukocyte counts and systemic inflammation markers in patients with asthma and obesity compared to those with asthma and BMI < 30 [18], when searching for predictors of a good response to inhalation corticosteroids (ICS) in patients with asthma and obesity.

Similar results were obtained in our study, as according to the SGRQ questionnaire, patients with ACO and T2DM had more severe symptoms, a stronger impact, and a higher total score than patients with COPD and T2DM.

Zysman et al. emphasized that in a cohort of patients with stable COPD, severe hypoxemia was associated with worse prognosis, more severe symptoms, greater airway obstruction, and hyperinflation. The authors also found that patients with severe hypoxemia (PaO_2 < 60 mmHg) and FEV_1 > 50 % were older, had higher BMI, and were more likely to be diagnosed with diabetes than patients with PaO_2 < 60 mmHg and FEV_1 < 50 %, highlighting the role of obesity [19].

In a systematic review and meta-analysis by J. Peng et al. in 2022, it was claimed that patients with ACO had lower FEV_1 compared to patients with asthma only, but the opposite result was found compared to patients with COPD alone [20]. Although there are conflicting reports that in patients with ACO, FEV_1 and FVC were lower than in COPD before bronchodilator testing [21]. In our study, a lower FEV_1 was established in the group of ACO patients with the presence of concomitant T2DM compared to the other two groups, but with a statistically significant difference only from the asthma + T2DM group.

In a Spanish study published in 2023, when comparing limitations in daily activities in patients over 65 years of age with asthma, COPD, or ACO, a lower percentage of patients in the third group had no limitations, and a higher percentage had limitations in performing heavy housework and cooking. On the other hand, there was no statistically significant difference in performing basic daily activities, and taking a shower was the most limited activity (18 %) and caused the most difficulty [23]. We found a significant dif-

Table 1. Clinical features of examined patients

Indicators, unit of measurement	Group 1 (n = 24)	Group 2 (n = 21)	Group 3 (n = 24)	p
Age, years	60 [10]	64 [4]	61.5 [19]	
Male Female	18 (75) 6 (25)	18 (85.7) 3 (14.3)	18 (75) 6 (25)	
Ever smoker	16 (66.66)	15 (71.4)	12 (50)	
Pack-years (among all)	8 [35]	10 [20]	4 [20]	NS
Pack-years (among smokers)	15 [36.75]	10 [10]	20 [24]	NS
Exacerbation frequency, per year	2.5 [2.5]	1 [1.5]	1 [2.5]	NS (p_1 = 0.085; p_3 = 0.064)
BODE index	5.5 [3.75]	4 [2]	4 [3.5]	NS
mMRC	3 [1.5]	3 [2]	2 [1.75]	NS
CAT	23.5 [5.5]	–	20 [7]	NS
ACQ	2.6 [0.95]	2.3 [0.85]	–	p_1 = 0.056
SGRQ total	65.09 [26.37]	46.67 [39.31]	48.91 [27.7]	p_1 = 0.054; p_3 = 0.001
SGRQ symptoms	75.39 [8.92]	67.97 [24.54]	48.48 [16.77]	p_3 < 0.001
SGRQ activity	73.435 [33.36]	52.98 [49.0]	60.61 [41.29]	p_1 = 0.042
SGRQ impact	56.84 [28.1]	39.26 [36.99]	42.36 [23.02]	p_1 = 0.04; p_3 = 0.039
BMI, kg/m^2	35.85 [6.62]	31.8 [10.5]	30.8 [4.02]	p_3 = 0.001
Fat, %	30.85 [16.225]	31.3 [9.5]	29.2 [13.575]	NS
Trunk fat, %	32.8 [10.15]	33.5 [12]	31 [7.425]	NS
Muscle mass, kg	67.45 [14.625]	64.7 [15.7]	58 [17.475]	p_3 = 0.001
FEV_1, %	41.315 [33.1]	50.86 [20.95]	49.405 [28.78]	p_1 = 0.027
FVC, %	44.215 [37.7]	56.97 [10.72]	59.015 [32.13]	NS
SVC, %	30.94 [25.57]	46.7 [19.775]	43.95 [22.0675]	p_1 = 0.021
Fasting glucose, mmol/L	8.45 [1.875]	7 [1.8]	6.9 [1.42]	p_3 = 0.028
HbA1c, %	8 [2.1]	7.8 [1.6]	9 [1]	p_2 = 0.037
Insulin, mIU/L	27.2 [17.9]	31.25 [13]	19.88 [7.59]	p_2 = 0.001
HOMA-IR index	11.2 [4.75]	11.59 [5.88]	7.81 [9.87]	NS
6-minute walk test	290 [127.5]	320 [160]	330 [100]	p_2 = 0.274; p_3 = 0.054

Notes: data are presented as Me [IQR] or n (%); NS — not significant; p_1 — the difference between groups 1 and 2; p_2 — the difference between groups 2 and 3; p_3 — the difference between groups 1 and 3.

ference between groups when comparing activity and impact scales according to the SGRQ. The results of the 6-minute test indicate a possible lower submaximal tolerance to physical activity and the ability to perform daily functions in patients in the first group, although statistically significant differences were not detected (p = 0.0548).

G. Yang et al. emphasize that metabolic dysfunction and insulin resistance are associated with the risk and severity of asthma, as HbA1c was associated with hospitalizations for asthma and inversely correlated with FEV_1 and FVC in a cohort of patients with asthma without DM [14].

The main mechanisms linking asthma and T2DM are chronic low-grade inflammation, obesity, hyperinsulinemia, diabetic pneumopathy, and oxidative stress [24–26].

N. Ghosh et al. investigated the metabolomic and systemic inflammatory profile of patients with ACO and found increased energy and metabolic load, significant changes in 11 metabolites including glucose dysregulation, compared to asthma and COPD. These markers and metabolites demonstrated significant correlations with each other and with lung function parameters [27–29].

K.N.C. Duong et al. [30] in a systematic review indicate that fasting glucose is the best diagnostic criterion for establishing a diagnosis of diabetes compared to HbA1c and the oral glucose tolerance test. At the same time, M. Wang et al. [31] conclude that HbA1c is a useful marker of glycemic control as a complement, as it does not take into account daily glycemic fluctuations that are associated with the development of complications [32, 33]. Therefore, in our study, the highest fasting glucose levels were observed in patients with ACO and T2DM, but there was no statistically significant difference in HbA1c.

Conclusions

Patients with asthma-COPD overlap and comorbid type 2 diabetes mellitus have worse quality of life, lower FEV_1 and SVC, submaximal exercise tolerance, higher fasting glucose levels, and a tendency towards increased exacerbation frequency.

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Особливості клінічного перебігу перехресту бронхіальної астми та хронічного обструктивного захворювання легень із супутнім цукровим діабетом 2-го типу

Резюме. ***Актуальність.*** Профілі коморбідності є досить частим предметом вивчення в пацієнтів із перехрестом бронхіальної астми та хронічного обструктивного захворювання легень (ХОЗЛ). Однак у випадку супутнього цукрового діабету 2-го типу (ЦД2) прицільних досліджень щодо якості життя, клінічного перебігу та функції зовнішнього дихання бракує. ***Мета дослідження:*** вивчити особливості клінічного перебігу перехресту астми та ХОЗЛ із супутнім ЦД2. ***Матеріали та методи.*** Обстежено 69 пацієнтів: 24 — з перехрестом астми та ХОЗЛ і ЦД2 (перша група), 21 особи з астмою та ЦД2 (друга група), 24 — з ХОЗЛ та ЦД2 (третя група). Діагноз перехресту астми та ХОЗЛ встановлювали згідно з рекомендаціями GINA та GOLD (2017). Оцінювали якість життя за опитувальниками CAT, ACQ, SGRQ, вираженість задишки — за шкалою mMRC, тяжкість перебігу та прогнозу захворювання — за індексом BODE. Проведено спірометрію з бронходилатаційним тестом, 6-хвилинний тест ходьби та біоімпедансний аналіз. ***Результати.*** Пацієнти основної групи отримали вищу загальну оцінку SGRQ, ніж пацієнти третьої групи (на 33 %, p = 0,001). Вищий показник ACQ та загальна оцінка SGRQ свідчать про тенденцію до гіршого контролю астми та нижчу якість життя в пацієнтів із перехрестом астми й ХОЗЛ та ЦД2 порівняно з групою астми й ЦД2 (p = 0,056 і p = 0,054 відповідно). Індекс маси тіла був вищим, ніж у пацієнтів із ХОЗЛ та ЦД2 (на 16,3 %, p = 0,001). Виявлено вищий уміст глюкози у сироватці крові натще, ніж у пацієнтів із ХОЗЛ та ЦД2 (на 18,3 %, p = 0,028). Об'єм форсованого видиху за першу секунду у групі перехресту астми й ХОЗЛ та ЦД2 був нижчим, ніж при астмі та ЦД2 (на 18,7 %, p = 0,027), а повільна життєва ємність легень зменшилася на 33 % (p = 0,021). Виявлена тенденція до нижчого результату 6-хвилинного тесту ходьби в основній групі порівняно з третьою (p = 0,0548) та вищої частоти загострень за рік, ніж у другій (p = 0,08) та третій групах (p = 0,06). ***Висновки.*** У пацієнтів із перехрестом астми та ХОЗЛ і супутнім цукровим діабетом 2-го типу спостерігаються гірші параметри якості життя, нижчий об'єм форсованого видиху за першу секунду та менша повільна життєва ємність легень, субмаксимальна переносимість фізичного навантаження, вищі показники глюкози натще, а також тенденція до збільшення частоти загострень.

Ключові слова: бронхіальна астма; хронічне обструктивне захворювання легень; перехрест астми та ХОЗЛ; цукровий діабет 2-го типу; коморбідність; якість життя; функція зовнішнього дихання