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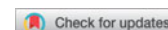
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Menopausal asthma—much ado about nothing? An observational study

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ABSTRACT

Objective: Menopausal asthma is considered a distinct asthma phenotype. Our aim was to identify potential specific features of asthma in postmenopausal women in a cohort of Polish females. **Methods:** Asthma severity and control, pulmonary function, exhaled nitric oxide (FE_{NO}), peripheral blood and induced sputum (IS) differential cell count were compared in three groups: women with premenopausal asthma (group 1), menopausal women with pre-existing asthma (group 2A) and menopausal women with asthma onset in the perimenopausal or menopausal period (group 2B). **Results:** We enrolled 27 women to group 1, 13 to group 2A and 16 to group 2B. Asthma severity and control, blood eosinophil count and FE_{NO} did not differ among the groups. Menopausal women had a higher incidence of irreversible airway obstruction (84.6% in group 2A and 56.2% in group 2B vs. 22.2% in group 1, $p < 0.001$ and $p = 0.03$, respectively). The proportion of patients with sputum eosinophilia was highest in menopausal women with pre-existing asthma, although the difference did not reach statistical significance (88.9% in group 2A vs. 66.7% in group 2B and 65.0% in group 1, respectively, $p = 0.86$). **Conclusions:** Menopausal women with asthma are characterized by an increased incidence of irreversible airway obstruction regardless of disease duration. This may indicate that age may contribute to pulmonary function impairment in asthmatic women independently of their hormonal status at the time of asthma diagnosis. Our results failed to confirm the presence of specific asthma features which would allow to distinguish the phenotype of menopausal asthma.

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Introduction

The concept of asthma phenotypes (defined as specific traits resulting from the interaction between the genotype of the individual and the environment) and endotypes (understood as a set of biological pathways identified as the mechanism leading to the observed asthma phenotype) has been evolving for many years and reflect the heterogeneity of the disease (1). Menopausal asthma, i.e., asthma with an onset in the perimenopausal or menopausal period has been proposed as a distinct disease phenotype characterized by neutrophilic airway inflammation and other features of severe asthma (2), including the necessity of treatment with high doses of inhaled corticosteroids (ICS) and frequent exacerbations. A high frequency of disease exacerbations in asthmatic peri/postmenopausal women was found in the Spanish FRIAM study, which showed that the female/male hospitalization ratio due to asthma increased with age and reached its peak in the age group of 40–60 years (3). This was confirmed by Zein et al., who analyzed data on asthma-related hospitalizations in the USA. These

authors reported a bi-modal age-gender distribution with most frequent hospitalizations in boys <10 years of age and women aged 40–60 years (4).

Women predominate among patients with late-onset asthma, although it is not clear if this phenomenon is not influenced by a gender bias. This might be related to the observations that physicians are more likely to diagnose chronic obstructive lung disease (COPD) in men and asthma in women when diagnosing patients with dyspnea and wheezing (5,6). Late-onset asthma develops in adult life, is usually non-allergic and is characterized by poor response to corticosteroid treatment (7). Therefore, it requires differentiation with COPD which is characterized by onset in adulthood, absence of atopy, and poor response to inhaled corticosteroids. In two recent studies on late-onset asthma, women accounted for 86.0% and 82.2% of asthma patients (8,9). On the other hand, asthma incidence rate in women is affected not only by age, but also by hormonal status. In a longitudinal population-based study, Treibner et al. demonstrated that women in the transitional, early menopausal and menopausal

period who are not using hormonal replacement therapy (HRT) had a higher risk for new-onset asthma than non-menopausal women (10). Conversely, a group of French authors found that in postmenopausal women, exogenous estrogen use was associated with an increased frequency of newly diagnosed asthma (11). These findings were consistent with the results of the earlier Nurses' Health Study which demonstrated a 35% lower relative risk of asthma in postmenopausal women not using HRT compared to premenopausal women, whilst in postmenopausal ever/current or past HRT users this risk was increased (12). In a meta-analysis of the impact of the hormonal status on the incidence and prevalence of asthma in women, Zemp et al. found no significant association between asthma incidence/prevalence rates and menopause, but when the patients were stratified according to HRT use, there was an increased asthma incidence in HRT users compared to those who did not use HRT (13).

Data on the predominant inflammatory pattern in menopausal asthmatics are scarce and also equivocal. Late-onset asthma is generally considered to be rather neutrophilic (7,14). Meanwhile, Balzano et al. demonstrated a significantly higher sputum eosinophilia in women with asthma onset within a year from menopause when compared to menopausal women with asthma diagnosed at least 10 years before menopause. This suggested that menopausal asthma should be considered as a distinct asthma phenotype (15). In contrast, Foschino Barbaro et al. found that asthmatics at menopause had higher proportions of neutrophils in induced sputum (IS) than premenopausal women with asthma (2) indicating similarity to late-onset asthma.

Given the contradictory reports on the mutual relations between menopause and asthma, we undertook a study to characterize features of asthma with onset in the menopausal period in a sample of Polish women. Our secondary aim was to compare these features with the disease characteristics in women in reproductive age and menopausal women in whom asthma was diagnosed before menopause.

Material and methods

Study design

This observational study was performed in female patients with asthma. Patient evaluation included detailed medical history with special regard to asthma exacerbations, pulmonary function testing, peripheral blood and induced sputum (IS) cell count, measurement of fractional exhaled nitric oxide (FE_{NO}), and serum

sex hormone concentrations. In order to determine if distinct features of menopausal asthma may be identified, the basic clinical and laboratory data were compared in three groups: 1) premenopausal women (group 1); 2) menopausal women, in whom asthma was diagnosed before the perimenopausal period (group 2A); and 3) menopausal women, in whom asthma was diagnosed during or after the perimenopausal period (group 2B).

The study was approved by the institutional review board of the Medical University of Warsaw and all the patients signed an informed consent to participate.

Study group

The study was conducted in female patients with stable asthma recruited from the pulmonary outpatient clinic of the Public Central Teaching Hospital of the Medical University of Warsaw between 2010 and 2011. The inclusion criteria were as follows: age between 18 and 75 years, diagnosis of asthma (defined as a history of recurrent dyspnea and wheezing, a positive bronchial reversibility test or/and positive result of methacholine bronchial challenge) for at least 6 months before enrollment, lack of asthma exacerbation during the last 3 months and no treatment with estrogens or gestagens. The exclusion criteria comprised age <18 or >75 years, asthma exacerbation within 3 months prior to the study onset, hormone replacement therapy and/or a history of surgical oophorectomy and hysterectomy.

Definitions

Menopause was diagnosed when the patient reported amenorrhea for at least 12 months prior to enrollment (16). The perimenopausal (transitional) period was described as a 2-year time interval before or after the last menstruation (16), and therefore patients were considered to be in the perimenopausal period when: 1/they were 49–51 years of age regardless of the presence or absence of menorrhea or 2/≥51 years of age and had a menstruation within the last 12 months before enrollment. The selection of 51 years as a cut-off value for the age of menopause was based on the estimation of the age of natural menopause in a population-based sample of Polish women in a cross-sectional survey of middle aged women's health (WOMID) (17).

Women were assumed to be in the premenopausal (reproductive) period when having 10–14 periods per year (8) and were aged <49 years.

Menopausal asthma was defined as asthma diagnosed during the perimenopausal (transitional) period or after

menopause. Asthma diagnosed before the transitional period was labeled as premenopausal asthma.

Assessment of asthma control and atopic status

The diagnosis of asthma, its severity, and degree of control were established in accordance with the Global Initiative for Asthma report (7). Additionally, asthma control was assessed by Asthma Control Test (ACT) with permission for the use of the validated Polish version from the copyright owner (18). Atopic status was defined on the basis of medical history (symptoms of allergic rhinitis and/or conjunctivitis) and at least one positive result of allergic skin prick tests with common aeroallergens (Allergopharma, Reinbeck bei Hamburg, Germany) defined as the diameter of ≥ 3 mm greater than the positive control (19). The allergens used in skin prick testing included grass mix, birch, alder, hazel, plantain (*Plantago lanceolata*), cat, dog, *Alternaria*, *Cladosporium*, *Aspergillus*, *Dermatophagoides farinae*, and *Dermatophagoides pteronyssinus*.

Pulmonary function testing

Pulmonary function testing (PFT) comprised spirometry with bronchial reversibility testing (LungTest 1000, MES, Cracow, Poland) and body plethysmography (Vmax 22 Series/V6200Autobox, SensorMedics, Yorba Linda, USA). Bronchial reversibility testing was performed in all patients in whom airflow limitation was found at baseline. The measurements were performed in accordance with the recommendations of the American Thoracic Society (ATS) and European Respiratory Society (ERS) (20–22). Irreversible airway obstruction was defined as post-bronchodilator $FEV_1/FVC <$ lower limit of normal (LLN) (22). Reference equations from the Global Lung Function Initiative were used for the calculation of the predicted values (23).

Airway inflammation

The assessment of airway inflammation was based on the measurement of FE_{NO} and induced sputum examination. FE_{NO} measurements were performed with the chemiluminescence on-line technique (Niox, Aerocrine, Solna, Sweden) in accordance with the ATS/ERS recommendations (24) and the value of 25 ppb was considered as the upper limit of normal (25).

Induced sputum collection, processing, and analysis were performed as described previously (26–28). The cut-off values of 3% for eosinophils and 40% for neutrophils were applied to define the IS eosinophilic and neutrophilic inflammatory phenotype, respectively (29).

Measurements of serum sex hormone concentrations

Serum folliculin-stimulating hormone (FSH) and estradiol levels were measured using the electrochemiluminescence system ECLIA Cobas (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

Data are shown as median and interquartile range (IQR) or numbers and percentages. Statistical analysis was performed using Statistica 8.0 (StatSoft Inc, Tulsa, USA). Kruskal-Wallis test or chi square test was used to compare data between groups. The strength and direction of the relationship between two variables were measured with Spearman's rank correlation coefficient. A p value <0.05 was regarded statistically significant.

Results

Patient characteristics

The study involved 56 asthmatic women; median age 52 years (range 18–73 years). Among these, 27 (48.2%) were allocated to the group of patients with premenopausal asthma (group 1), 13 (23.2%) to the group of menopausal patients with pre-existing asthma (group 2A) and 16 (28.6%) – to the group of women with menopausal asthma diagnosed during or after the perimenopausal period (group 2B). The comparison of the basic characteristics of the three groups is presented in Table 1.

The number of patients with allergic asthma as well as the number of patients with self-reported aspirin-exacerbated respiratory disease (AERD) was similar in the three groups. The median absolute blood eosinophil count did not differ among the groups [0.26 (0.17 – 0.48) $\times 10^3/\mu\text{l}$, 0.25 (0.16 – 0.36) $\times 10^3/\mu\text{l}$ and 0.25 (0.21 – 0.42) $\times 10^3/\mu\text{l}$ in group 1, 2A, and 2B, respectively, $p = 0.46$].

Asthma severity and control

The vast majority of the investigated patients suffered from severe asthma (Table 2) and were treated with a medium/high daily dose of inhaled steroids [median daily dose of budesonide or equivalent 800 (400–1600) μg in group 1, 800 (400–1600) μg in group 2A and 800 (200–1600) μg in group 2B, respectively, $p = 0.21$]. Twenty one patients received leukotriene receptor antagonists (48.1% in group 1, 15.4% in group 2A and 37.5% in group 2B, respectively, $p = 0.004$). None of the patients were treated with biologic therapy, as it was unavailable in Poland at the time of the study.

Table 1. Comparison of the basic characteristics of the three subgroups of asthmatic women distinguished according to the predetermined criteria for age, hormonal status, and the presence or absence of menstruation. Group 1 – premenopausal women, group 2A – menopausal women with pre-existing asthma, group 2B – menopausal women in whom asthma was diagnosed during or after the perimenopausal period (menopausal asthma).

Variable	Group 1 (n = 27)	Group 2A (n = 13)	Group 2B (n = 16)	P
Age (years)	41 (31–45)	57 (56–60)	59 (56–63)	<0.001
BMI (kg/m ²)	24.1 (21.6–31.9)	27.5 (26.1–34.7)	28.3 (25.5–31.0)	0.29
Non smokers/Ex-smokers/Smokers	10/13/4	7/3/3	8/7/1	0.48
Smoking history (packyears)	2.5 (0–10)	0.0 (0–20)	0.05 (0.0–13.7)	0.13
Age of asthma diagnosis (years)	30 (18–39)	30 (25–35)	54 (51–57)	≤0.001
Duration of asthma (years)	6 (2–11)	30 (25–36)	3.5 (2–8)	≤0.001
Allergic asthma n (%)	18 (66.7)	8 (61.5)	10 (62.5)	0.94
AERD n (%)	6 (22.2)	0	4 (25.0)	0.16
Serum estradiol (pg/ml)	82.1 (39.3–168.9)	3.6 (2.7–4.5)	10.5 (4.1–16.1)	≤0.001
FSH (IU/l)	6.0 (3.9–7.5)	68 (48.7–98.2)	68 (38.2–86.0)	≤0.001

Note. Data presented as median and IQR. BMI = body mass index; AERD = aspirin exacerbated respiratory disease; FSH = folliculin stimulating hormone.

Asthma control was comparable in all the three groups (Table 2). The median number of exacerbations in all the patients was 2 per year (0–10) and it did not differ among the three investigated subgroups – 3 (1–5) exacerbations per year in group 1 vs. 2 (0.5–3) in group 2A and 2.0 (0.0–3.0) in group 2B, respectively, $p = 0.18$).

Pulmonary function testing

There were significant differences in pulmonary function among the groups with the lowest baseline FEV₁ and highest baseline values for lung hyperinflation and gas trapping in women from group 2A (Table 3). Pre-bronchodilator spirometric parameters were comparable in groups 1 and 2B; however, we found a higher incidence of irreversible airway obstruction in the latter (22.2% vs. 56.2%, respectively, $p = 0.026$). This was

Table 2. Asthma severity and control in the investigated groups according to the GINA 2017 criteria (5). Group 1 – premenopausal women, group 2A – menopausal women with pre-existing asthma, group 2B – menopausal women in whom asthma was diagnosed during or after the perimenopausal period (menopausal asthma).

	Group 1 (n = 27)	Group 2A (n = 13)	Group 2B (n = 16)	P
Asthma severity				
Episodic asthma	0	0	0	1.0
Mild asthma n (%)	5 (18.5)	0	2 (12.5)	0.25
Moderate asthma n (%)	4 (14.8)	2 (15.4)	4 (25.0)	0.68
Severe asthma n (%)	18 (66.7)	11 (84.6)	10 (62.5)	0.39
Asthma control				
Well controlled asthma n (%)	3 (11.1)	0	1 (6.3)	0.44
Not well-controlled asthma n (%)	13 (48.2)	8 (61.5)	10 (62.5)	0.58
Poorly controlled asthma n (%)	11 (40.7)	5 (38.5)	5 (31.2)	0.82
ACT score (points)	18 (14–22)	16 (8–22)	21.5 (2–8)	0.21

Note. ACT = Asthma Control Test; ACT score presented as median (IQR).

also the case when group 1 was compared with group 2A (22.2% vs. 84.6%, respectively, $p < 0.001$). The incidence of irreversible airway obstruction was comparable in groups 2A and 2B ($p = 0.11$). In these two groups, airway obstruction was irreversible in all the patients who presented with FEV₁/FVC < LLN at baseline; none of the patients had reversible airway obstruction. Moreover, we also found higher values of pre- and post-bronchodilator RV, TLC and RV/TLC in groups 2A and 2B, when compared to group 1 (Table 3). Again, no differences in these values between groups 2A and 2B were found.

There was a significant inverse correlation between baseline FEV₁ (% predicted) and serum FSH in women from group 2B ($r = -0.54$, $p = 0.04$). This correlation was not observed in the two other groups. RV and RV/TLC also correlated with FSH ($r = 0.53$, $p < 0.001$ and $r = 0.56$, $p < 0.001$ for baseline values and $r = 0.38$, $p = 0.03$ for post-bronchodilator values, respectively) and estradiol ($r = -0.45$, $p < 0.001$ and $r = -0.49$, $p < 0.001$ for baseline values and $r = -0.70$ for baseline and $r = -0.59$ for post-bronchodilator values, $p < 0.001$ for both, respectively) in the whole group, but these correlations failed to reach statistical significance in sub-analyses for individual groups. In group 2B, both pre- and post-bronchodilator RV/TLC correlated with blood absolute eosinophil count ($r = 0.53$, $p = 0.04$ and $r = 0.68$, $p = 0.03$, respectively); this was also the case in group 1 ($r = 0.40$, $p = 0.04$ and $r = 0.69$, $p = 0.03$, respectively). In group 1, a positive correlation was also noted between blood eosinophil count and pre- and post-bronchodilator RV % predicted ($r = 0.48$, $p = 0.02$ and $r = 0.68$, $p = 0.02$, respectively).

We did not find correlations between lung function (both pre- and post-bronchodilator) and IS eosinophils or neutrophils and FE_{NO} in the group as a whole or in any of the investigated subgroups.

Table 3. Comparative analysis of spirometry and selected lung volumes in the investigated groups. Basic spirometric values taken from post-bronchodilator spirometry when applicable. Irreversible airway obstruction was defined as post-bronchodilator FEV₁/FVC < LLN. Group 1 – premenopausal women, group 2A – menopausal women with pre-existing asthma, group 2B – menopausal women in whom asthma was diagnosed during or after the perimenopausal period (menopausal asthma).

Variable	Group 1 (n = 27)		Group 2A (n = 13)		Group 2B (n = 16)		p
	Baseline	PB (n = 12)	Baseline	PB (n = 11)	Baseline	PB (n = 9)	
FEV ₁ (% predicted)	79.8 (63.8–95.7)	82.9 (76.4–87.6)	61.6 (48.5–82.6)	69.2 (61.5–85.6)	68.80 (57.3–82.4)	75.9 (65–85.1)	* 0.02 # 0.41
FVC (% predicted)	93.0 (80.5–101.6)	92.4 (84.6–104)	92.2 (72.4–97.4)	98.5 (85.7–103.7)	85.8 (80.7–96.9)	96.2 (79.8–102.2)	* 0.30 # 0.85
FEV ₁ /FVC (%)	72.4 (71.3–76.7)	72.9 (71.8–77.9)	62.8 (56.2–66.4)	62.0 (56.4–65.4)	63.8 (62.7–70.0)	65.3 (61.4–68.2)	* 0.003 # 0.002
RV (% predicted)	110.1(104.2–116.2)	119.9 (93.1–141.5)	124.5(116.6–130.7)	151.2 (124.5–169.3)	116.3 (109.3–124.0)	140.7 (137–159.1)	* 0.001 # 0.05
TLC (% predicted)	125.1 (102.3–137.5)	107.3 (94.9–111.6)	159.4 (138.7–196.2)	123.3 (11.4–134.9)	149.8 (119.7–165.7)	115.9 (105.2–122.5)	* 0.003 # 0.02
RV/TLC %	35.4 (29.8–40.5)	35.4 (32.4–40.9)	49.2 (42.7–62.3)	46.9 (36.5–53.0)	47.9 (40.5–56.3)	48.8 (44.9–52.3)	* ≤0.001 # ≤0.001
Normal result of spirometry n (%)	15 (55.6)		2 (15.4)		7 (43.8)		0.55
Irreversible airway obstruction n (%)	6 (22.2)		11 (84.6)		9 (56.2)		0.03

Note. Data presented as median (IQR) when applicable. FEV₁ = forced expiratory volume at 1st second; FVC = forced vital capacity; TLC = total lung capacity; RV = residual volume; PB = post-bronchodilator value. *p value for comparison of baseline parameters (Kruskal–Wallis test); #p value for comparison of post-bronchodilator parameters (Kruskal–Wallis test).

Airway inflammation

The median value of FE_{NO} in the whole group was 21.6 (4.8–109) ppb, and no differences in FE_{NO} were found among the investigated subgroups [15.6 (11.0–34.8) ppb in group 1, 20.2 (13.3–38.1) ppb in group 2A and 24.4 (19.1–34.5) ppb in group 2B, respectively, $p = 0.64$]. The proportions of patients with FE_{NO} >25 ppb were also comparable in the three groups (33.3% in group 1, 30.7% in group 2A and 37.7% in group 2B, respectively, $p = 0.93$).

Induced sputum was obtained from 44/56 patients (78.6%)—20/27 (74.1%) in group 1, 9/13 (69.2%) in group 2A and 15/16 (93.8%) in group 2B, respectively. There were no differences in IS eosinophil and neutrophil absolute count (Table 4). Women with IS eosinophilic inflammatory pattern accounted for 70.5% of the women in whom IS could be obtained and the proportion of women with sputum eosinophilia was highest in group 2A, but the difference did not reach statistical significance. Similarly, the proportion of women with sputum neutrophilia was numerically highest in group 2B; however, the difference in the incidence of neutrophilic inflammatory pattern among the three investigated groups was not statistically significant (Table 4).

We did not find correlations between FE_{NO} and serum FSH and estradiol concentrations, ACT score and the number of exacerbations in any of the investigated groups. Such correlations were also not demonstrated for IS neutrophil or eosinophil absolute count and proportion.

Discussion

Our results showed that menopausal women are more likely to present with irreversible airway obstruction than premenopausal asthmatic women. Women after menopause were also characterized by more pronounced functional features of gas trapping when compared to women in the reproductive period, and this was irrespective of asthma duration. We failed to demonstrate differences in asthma severity and control, exacerbation frequency as well as in the type of airway inflammatory pattern between women before and after menopause.

The lack of differences in asthma severity and control between pre- and menopausal women is in contrast with earlier reports. Balzano et al. who showed a higher incidence of eosinophilic pattern of airway inflammation in women with menopausal asthma and demonstrated a correlation of sputum eosinophilia and exacerbation rate in a one year follow-up (15). As mentioned

Table 4. Selected parameters of induced sputum in the investigated patients. Group 1 – premenopausal women, group 2A – menopausal women with pre-existing asthma, group 2B – menopausal women in whom asthma was diagnosed during or after the perimenopausal period (menopausal asthma).

Parameter	Group 1 (n = 20)	Group 2A (n = 9)	Group 2B (n = 15)	P
IS absolute eosinophil count	13.0 (6.0–32.0)	22.50 (11.5–33.5)	26.0 (7.0–32.0)	0.65
IS absolute neutrophil count	26.0 (4.0–42.0)	10.0 (8.0–28.5)	32.0 (12.0–56.0)	0.48
Proportion of patients with IS eosinophilia* n (%)	13 (65.0)	8 (88.9)	10 (66.7)	0.86
Proportion of patients with IS neutrophilia** n (%)	4 (20.0)	2 (22.2)	5 (33.3)	0.77

Note. Data presented as median (IQR). IS = induced sputum. *IS eosinophils > 3%, **IS neutrophils > 40%.

previously, asthma-related hospitalizations are most frequent in women aged 40–60 years (3,4). However, in the two studies analyzing hospitalization rates in asthmatics, the relationship between asthma exacerbations and menopause are only assumptive, as hormonal status was not assessed. The FRIAM study showed that except for female gender, there were two other factors increasing the number of hospitalizations in this age group, namely obesity and nasal polyposis (3). Baptist et al. who compared adults with asthma of long duration and adults with late-onset asthma found that, although the latter experienced more frequent hospitalizations, the number of asthma-related urgent care visits and oral steroid use in the past year did not differ significantly between the two investigated groups (8).

None of the menopausal women with $FEV_1/FVC < LLN$ at baseline presented with reversible airway obstruction. The high incidence of irreversible airflow limitation in our older patients is in accordance with the results of Tay et al. who found that that age was the only variable independently associated with chronic airflow limitation in a cohort of never-smoking patients with asthma (30). These authors also reported that 63.2% of patients with chronic airflow limitation were diagnosed with late-onset asthma. Ponte et al. found that the probability of irreversible airway obstruction in asthmatics aged 40–65 years was more than two-fold higher than in asthmatics aged <40 years and further increases with age; women comprised 83% of this investigated age group (31). In our analysis, patients with irreversible airway obstruction defined as post-bronchodilator $FEV_1/FVC < LLN$ accounted for 69.0% of the group of menopausal women (group 2A and 2B) and 22.2% of the premenopausal women, respectively. On the other hand, Baptist et al. demonstrated that, although patients with late-onset asthma were more likely to have severe disease than patients with long-standing asthma, there were no differences between these groups in terms of spirometry (8). Furthermore, Herscher et al. showed that patients with late-onset asthma were less likely to have airflow limitation (defined as $FEV_1/FVC < 70\%$) than patients with asthma of long duration (9). Again, in both mentioned studies there was a marked female predominance in the investigated groups. However, both of these studies provide data on spirometry itself, without specifying if it had been performed after the intake of any inhaled medication and do not mention bronchial reversibility testing.

Another factor that could have contributed to the differences in the pulmonary function in our patients is the hormonal status. In a large multicenter population-based study involving nine European countries, Real et al. found that women with amenorrhea for >6 months had

lower FEV_1 and FVC and reported more respiratory symptoms than those with menstruations, and this difference was irrespective of smoking status (32). Triebner et al. showed that both FEV_1 and FVC decline more rapidly in transitional and menopausal women than in women with regular menstruations (33). In our study, FEV_1 correlated inversely with serum FSH in the whole group, but a sub-analysis did not confirm such a correlation in premenopausal women and in menopausal women with pre-existing asthma and showed this relationship only in women with asthma onset after menopause. FEV_1 was lowest in the group of menopausal women with pre-existing asthma what, together with the highest proportion of patients irreversible airway obstruction (84.6%), longest asthma duration (median 30 years) in this group and a similar serum FSH when compared to menopausal asthmatics with disease onset after menopause, suggests that disease duration (and not the age of disease onset or hormonal status) is one of the most relevant factors contributing to lung function impairment in women with asthma. Our findings on the negative impact of high FSH and low estradiol levels on lung volumes are difficult to compare with the results of other authors because, as to our knowledge, no studies have addressed this issue. However, the highest indices of gas-trapping observed in menopausal women with pre-existing asthma, also suggest that disease duration is a crucial factor contributing to lung function impairment in asthmatic women after menopause. This may be attributed to the reduction in lung elastic recoil related not only with age but also with long-standing asthma (34,35).

There are conflicting data on the type of airway inflammation which occurs in menopausal asthmatic women. Foschino Barbaro et al. reported a significantly higher percentage of sputum neutrophils along with a trend towards higher values of interleukin 6 in exhaled breath condensate in asthmatics after menopause compared to premenopausal patients (2). At the same time, these authors reported a positive correlation between serum estradiol and the percentage of neutrophils in IS. As menopause is characterized by low serum estradiol levels, this finding is in contrast with the hypothesis that asthma in menopause is related with sputum neutrophilia. Balzano et al. reported an eosinophilic pattern with an approximately 6-fold higher mean IS absolute eosinophil count in women with asthma onset after menopause compared to menopausal women with pre-existing asthma ($19.5 \pm 10.8\%$ vs. $3.3 \pm 4.3\%$, respectively, $p < 0.001$) (3). In our study, we did not find differences in the IS absolute eosinophil and neutrophil count in the investigated subgroups. The proportion of women with sputum eosinophilia was highest in menopausal women

with pre-existing asthma; however, this difference did not reach statistical significance. Neither did we find differences among the groups in the incidence of sputum neutrophilia. This is in contrast with previous observations that menopausal asthma presents with a specific pattern of inflammation and supports the hypothesis that it may not be a distinct disease phenotype.

There are two major limitations to our study. Firstly, the investigated groups are relatively small. However, the low incidence rate of menopausal asthma, estimated to reach approximately 1.1–1.15/1000 person-years (13), may at least to some extent explain our objective difficulties in patient recruitment. We would like to emphasize that one of the most frequently cited reports on this topic is an analysis of 11 women with menopausal asthma and 9 menopausal women with pre-existing asthma (15). Secondly, the high proportion of severe asthma in all the three analyzed subgroups clearly indicates a selection bias. This is a result of the setting in which the study was conducted; our institution is a tertiary care center experienced in asthma management and asthmatics referred to our outpatient clinic are mainly patients with severe and/or difficult-to-treat asthma who require specialist care. It seems therefore that further studies in larger groups and different degrees of asthma severity (mild/moderate asthma in particular) are warranted. Recruitment from our outpatient clinic could have also influenced the age of the premenopausal patients with asthma as in our country, older patients usually seek medical care in public healthcare units due to economic reasons, while younger patients tend to rely on private healthcare service.

Conclusions

Our study showed that menopausal women with asthma are characterized by an increased incidence of irreversible airway obstruction regardless of disease duration. This suggests that age may contribute to pulmonary function impairment in asthmatic women independently of their hormonal status at the time of asthma diagnosis. Our results failed to confirm the presence of specific asthma features which would allow to distinguish the phenotype of menopausal asthma.

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