ORIGINAL ARTICLE

Assessment of airway remodeling by quantitative computed tomography at various degrees of asthma severity defined according to the Global Initiative for Asthma report: a single-center study

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KEY WORDS

airway remodeling, asthma, quantitative computed tomography

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ABSTRACT

INTRODUCTION In asthma, airway remodeling is defined as structural changes of the airways. The association between remodeling and asthma severity is still unclear, and there are limited data on the intensity of airway remodeling in various stages of the disease as defined in the Global Initiative for Asthma (GINA) asthma severity classification. Computed tomography (CT) and postprocessing applications are effective tools to assess the intensity of airway remodeling.

OBJECTIVES The aim of this study was to assess the severity of morphometric abnormalities of the respiratory tract in patients with various degrees of asthma severity according to the GINA guidelines.

PATIENTS AND METHODS The study included 70 patients with asthma and 29 healthy controls matched for age, sex, and body mass index. Patients were examined with a 128 multislice CT scanner at full inspiration. The measurements were made from the third to the ninth generations of bronchi. Bronchial parameters were compared between patients with severe and nonsevere asthma and healthy controls.

RESULTS We found no differences in the thickness of the bronchial wall, percentage of the wall area, inner and outer bronchial diameters, and the size of the bronchial lumen between severe and nonsevere asthma groups. Significant differences were noted in the thickness of the bronchial wall and the percentage of the wall area between the severe asthma group and the control group ($P < 0.017$) as well as between the nonsevere asthma group and controls ($P < 0.017$).

CONCLUSIONS Our findings indicated similar values of CT morphological measures of airway remodeling in all asthma severity groups as defined by the GINA guidelines.

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INTRODUCTION Despite the advances in knowledge and new treatments, asthma remains a major concern worldwide. The goals of asthma treatment are set out in many international and national recommendations and include achieving and maintaining asthma control and reducing future risks, notably asthma-related deaths, exacerbations, and progressive airway damage.[1-3]

Asthma is a chronic inflammatory disease of the airways. Inflammation results from the activation of the immune system by an allergic or nonallergic mechanism. The phenotype and clinical presentation of asthma are driven by an endotype, that is, an inflammatory mechanism. Until today, there have been 2 clearly defined groups of endotypes—type 2 high and type 2 low endotypes.[4-6] Different molecular inflammatory endotypes correspond with the response to treatment with biological therapies and are the basis of personalized medicine. Independently of the specific molecular

WHAT'S NEW?

Asthma is one of the most common lung diseases, but its pathophysiology is still not fully understood. Airway remodeling in asthma refers to structural changes of the airways. The relationship between airway remodeling and asthma severity remains under investigation, and data on the intensity of remodeling at various degrees of the disease severity according to the Global Initiative for Asthma classification are still scarce. With the use of advanced postprocessing software and multislice computed tomography, it is possible to perform detailed measurements of the bronchial tree. This study revealed a similar intensity of morphological changes in computed tomography scans in all examined patients with asthma, regardless of the disease severity. These interesting results may implicate that airway remodeling begins early in the course of asthma, also in mild and moderate stages of the disease.

pathomechanism, inflammation of the airways is traditionally considered to be associated with hyperresponsiveness and remodeling of the airways. Remodeling refers to structural changes in the airways that include subepithelial fibrosis, basal membrane thickening, increased smooth muscle mass, enlargement of the glands, neovascularization, and epithelial alterations.[7] The relationship between the remodeling pattern, clinical presentation, different phenotypes / endotypes, and specific molecular mechanisms of inflammation is unclear. Histological assessment of remodeling is methodologically difficult and requires the use of invasive techniques.[8] For over 20 years, computed tomography (CT) has been a convenient tool for the assessment of the intensity of airway remodeling.[9,10] The most widely used quantitative CT (qCT) parameters to assess bronchial wall remodeling include wall thickness (WT), wall area percentage (WA%), lumen area (LA), as well as the outer and inner diameter of the bronchus. The influence of airway remodeling on lung function has been postulated, and this relationship is still under investigation.[11] In a previous study, a significant increase in airway thickness in patients with asthma compared with healthy individuals was shown.[12]

It is believed that remodeling is associated with the severity of asthma and is related to impaired lung ventilation.[8,13] Evaluation of airflow limitation is obviously an important part of asthma assessment; however, a more complex approach to determining asthma control and severity has been recommended over the last years. It is based on the analysis of symptoms and treatment strength, not lung function.[14] However, data on the incidence and intensity of airway remodeling at various levels of asthma severity as defined in the Global Initiative for Asthma (GINA) classification are still sparse.

The aim of our study was to assess the severity of morphometric abnormalities of the respiratory tract using qCT in patients with various degrees of asthma severity according to the GINA guidelines.

PATIENTS AND METHODS

Patient characteristics

This was an observational study performed at a single academic center. We enrolled 83 patients with asthma (49 women and 34 men) and a control group of 30 healthy volunteers (12 women and 18 men) matched for sex, age, body mass index, and body surface area (calculated using the Mosteller formula). All patients were consecutively recruited at the outpatient allergology clinic of the Department of Internal Diseases, Pneumonology, and Allergology of the Wroclaw Medical University. None of the study participants have ever been smokers.

A definite asthma diagnosis established in childhood, adolescence or early adulthood was the main inclusion criterion. Asthma severity staging was performed in line with the 2015 GINA report and based on the severity of airflow limitation.[14] According to the GINA guidelines, the severity of asthma is assessed retrospectively, from the level of the treatment required to control the symptoms and exacerbations, and not from the level of airflow limitation. For this reason, the spirometric measurements were only used to describe the characteristics of the study groups and were not the basis for further analysis.

At enrollment, the study group consisted of 83 individuals and included patients with severe (n = 25), moderate (n = 28), and mild (n = 30) asthma. The mean (SD) age of individuals in the severe asthma (SA), moderate asthma, mild asthma, and control groups was 49 (9), 47 (16), 44 (13), and 47 (13) years, respectively. All patients were examined in a stable, controlled phase of asthma. The patients were asked to refrain from taking inhaled rescue bronchodilators for at least 8 hours and long-acting bronchodilators for at least 24 hours before the examination.

Healthy volunteers were recruited in the same outpatient clinic using nonprobability purposive sampling. The inclusion criteria for the control group comprised no history of respiratory disease, no major heart disease, and no other serious chronic diseases.

Imaging system errors (motion artifacts and incorrect reconstruction algorithms) as well as incidentally diagnosed comorbidities (sarcoidosis, lung tumor) resulted in the exclusion from the study.

Quantitative computed tomography

All patients were examined in the supine position at full inspiration and breath-holding, using a 128 multislice CT scanner (SOMATOM Definition AS+, Siemens Healthcare, Erlangen, Germany). Scans were analyzed and reconstructed using the Syngo.Pulmo3D software (Siemens Healthcare). Measurements of the bronchial tree from the third (segmental) to the ninth (subsegmental) generation were performed independently for each patient. The following qCT parameters were taken into account: WT, wall area (WA), WA%, ID, and LA. Measurements were carried out in a blind

TABLE 1 Patient characteristics

Parameter		SA (n = 22)	non-SA (n = 48)	HC (n = 29)	*P* value			
					SA vs HC[a]	Non-SA vs HC[a]	SA vs non-SA[a]	SA vs non-SA vs HC[b]
Age, y		49 (9)	45 (15)	47 (13)	–	–	–	0.53
		49 (41–58)	45 (35–58)	51 (38–58)				
Height, cm		165.5 (8.3)	171.2 (9.2)	172.7 (9.5)	0.007	0.41	0.02	0.018
		163.0 (159.8–172.8)	170.0 (164.0–179.3)	170.0 (164.5–181.5)				
Weight, kg		74.6 (16.8)	79.5 (18.8)	82.2 (16.5)	–	–	–	0.32
		74.5 (60.8–86.8)	76.5 (65.8–90.0)	83.0 (69.5–94.5)				
Sex, n (%)	Female	15 (68)	27 (56)	11 (38)	–	–	–	0.08[c]
	Male	7 (32)	21 (44)	18 (62)				
BMI, kg/m^2		27.1 (5.5)	27.0 (5.6)	27.5 (5.0)	–	–	–	0.19
		27.8 (23.1–30.1)	26.5 (22.9–30.4)	26.8 (24.0–31.0)				
BSA, m^2		1.8 (0.2)	1.9 (0.3)	2.0 (0.2)	–	–	–	0.14
		1.8(1.7–2.0)	1.9 (1.7–2.1)	2.0 (1.8–2.2)				
Asthma duration, y		25 (12)	20 (11)	N/A	–	0.14	–	–
		20 (10–28)	20 (18–31)					
FEV1, l		1.7 (0.5)	2.9 (1.0)	3.7 (1.1)	<0.001	0.004	<0.001	<0.001
		1.7 (1.4–2.0)	2.6 (2.3–3.6)	3.6 (2.6–4.6)				
FEV1, % predicted		63.3 (17.6)	90.8 (20.4)	108.2 (13.1)	<0.001	<0.001	<0.001	<0.001
		61.1 (51.6–76.6)	92.1 (77.6–101.9)	108.3 (100.6–117.7)				
FVC, l		3.1 (0.7)	4.2 (1.2)	4.7 (1.3)	<0.001	0.10	<0.001	<0.001
		3.1 (2.7–3.4)	4.2 (3.3–5.1)	4.7 (3.6–5.9)				
FVC, % predicted		93.6 (18.7)	110.1 (21.7)	115.9 (12.7)	<0.001	0.11	0.002	<0.001
		93.9 (77.6–108.1)	108.7 (96.9–122.5)	119.3 (108.3–122.8)				
FEV1/FVC%		57.1 (11.7)	69.1 (10.5)	77.5 (6.0)	<0.001	0.002	<0.001	<0.001
		58.4 (47.3–67.0)	70.7 (61.0–76.6)	77.1 (72.1–83.0)				

Data for each variable are presented as mean (SD) (upper line) and median (interquartile range) (lower line) unless indicated otherwise.

a The Bonferroni correction was applied for pairwise comparisons (Mann–Whitney test) and a *P* value <0.017 was considered significant.

b Variables compared using the Kruskal–Wallis test; a *P* value <0.05 was considered significant.

c Variables compared using the χ^2 test

Abbreviations: BMI, body mass index; BSA, body surface area; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HC, healthy controls; N/A, not applicable; non-SA, nonsevere asthma; SA, severe asthma

fashion by a single observer in the middle part of each bronchial generation.

Due to the lack of a significant difference in quantitative features of the bronchial tree (ID, WT, WA, WA%, and LA) between the mild and moderate asthma groups, a decision was made to combine these 2 groups into a single nonsevere asthma group (non-SA). All further analyses concerned the SA, non-SA, and control groups. The study groups differed in terms of height and airflow limitation. The SA group was characterized by a more severe airflow limitation compared with the non-SA and control groups (predicted percentage of forced expiratory volume in 1 s [FEV1%], 63.4%, 92%, and 108.4%, respectively). Detailed characteristics of the study and control groups are presented in TABLE 1. More details regarding the CT scanning protocol and measurement of the bronchial parameters are described in a study by Patyk et al.[12]

The study protocol was approved by the Bioethics Committee of the Wroclaw Medical University (no. 280/2014 and 92/2017). All participants provided written informed consent before the commencement of any study-related procedure.

Statistical analysis Statistical analysis was performed with the use of GraphPad Prism version 7.0 (GraphPad Software, San Diego, California, United States). Normality of distribution was determined with the Shapiro–Wilk test and the D'Agostina–Pearson omnibus normality test. Only variables that passed both tests of normality were considered to follow normal distribution. The χ^2 test was used to evaluate the frequency distribution in all 3 groups. Due to their size, the study groups were compared with the Mann–Whitney test. Comparisons between 3 groups (SA, non-SA, and controls) were performed using the Kruskal–Wallis test, and

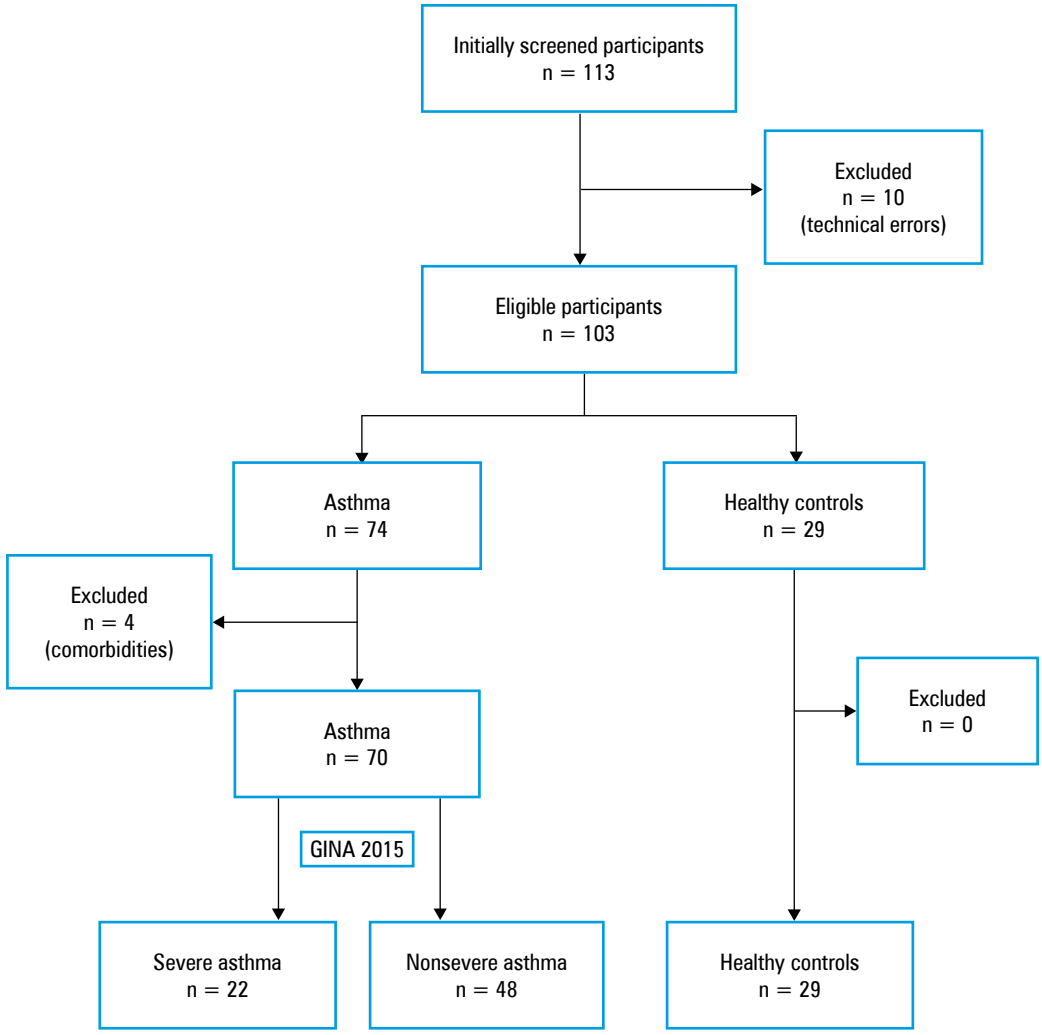

FIGURE 1 Study flowchart

a *P* value of less than 0.05 was considered significant. Pairwise comparisons (the Mann–Whitney test) were corrected for multiple testing using the Bonferroni correction, and a *P* value of less than 0.017 was considered significant. The Spearman *R* correlation coefficient was calculated to assess the correlation between the factors.

RESULTS The final analysis included 70 patients with asthma (22 in the SA group and 48 in the non-SA group) and 29 healthy controls. A total of 10 participants (9 patients with asthma and 1 healthy volunteer) were excluded from the quantitative image reconstruction analysis due to CT motion artifacts and reconstruction errors. Four patients with asthma were additionally excluded due to the detection of diseases other than asthma in the CT examination. A detailed study flowchart is presented in FIGURE 1. Except for single measurements, all airway segmentation and image reconstruction data from the third to the sixth generation of bronchi were available in all examined patients (n = 99). Data for the seventh, eighth, and ninth bronchial generations were attainable in 95% (n = 94), 83% (n = 82) and 63% (n = 62) of participants, respectively. There was no significant difference (the χ^2 test) in the number of bronchial generation measurements achieved between the study and control groups. All 3 groups did not differ in terms of demographic or physical characteristics, with the exception of height. Patients in the SA group were shorter (165.5 cm) than patients in the non-SA (171.2 cm) and control (172.7 cm) groups ($P = 0.018$). No relationship between any morphological features of airway remodeling and demographic or physical characteristics, including height, was found.

There were no differences with regard to most of the qCT parameters, that is, WT, WA%, ID, and LA between the SA and non-SA groups. Differences between the study groups were numerically small, and their occurrence was changeable, inconsistent, and not significant. However, some significant differences ($P < 0.017$) were noted in terms of WT and WA% between the SA group and the control group as well as between the non-SA group and controls. Both parameters had greater values in the asthma groups. The differences in WT and WA% are presented in FIGURE 2 and FIGURE 3, respectively. Details regarding the WT and WA% values are presented in Supplementary material,

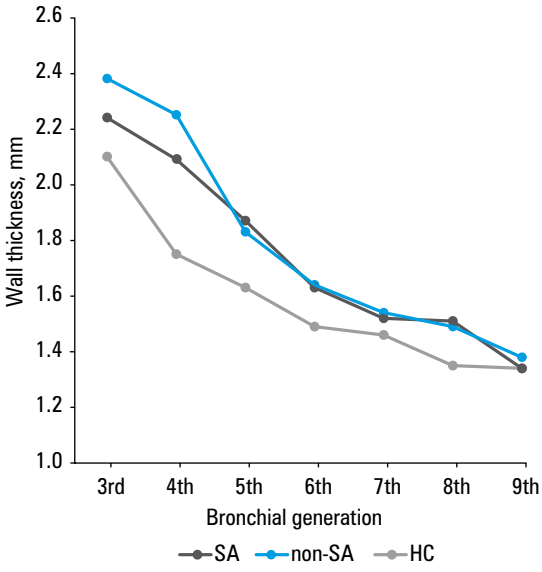

FIGURE 2 Wall thickness of the bronchial tree generations in patients with severe asthma (SA), non-severe asthma (non-SA), and healthy controls (HC)

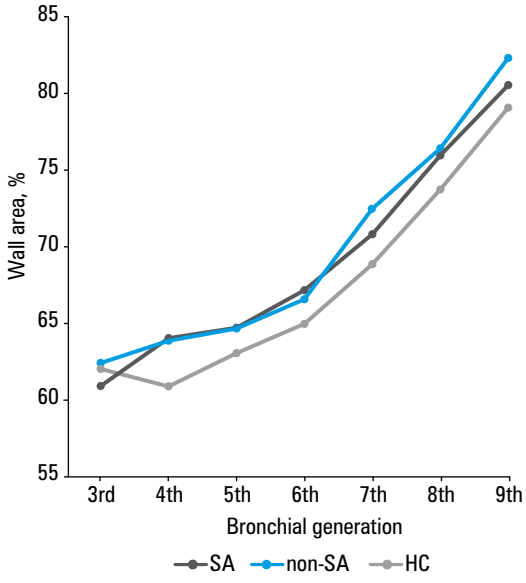

FIGURE 3 Wall area percentage of the bronchial tree generations in patients with severe asthma (SA), non-severe asthma (non-SA), and healthy controls (HC)

Table S1. Neither of these parameters correlated with the predicted FEV1%, predicted forced vital capacity (FVC) or the absolute value of the FEV1 to FVC ratio in all studied groups (all $P > 0.05$). Patients in the SA and non-SA groups did not differ in terms of disease duration. The mean (SD) duration of asthma in each group was 25 (12) and 20 (11) years, respectively ($P = 0.14$).

DISCUSSION Airway remodeling in asthma is a structural change of the airways that can be observed and measured using high-resolution CT. Differences in the thickness of bronchial walls and the lumen of the airways in patients with asthma and healthy individuals were documented in many studies.[12,15] Due to technical limitations in the past, most studies assessed airways up to the fifth or sixth generation of bronchi[15-17]; however, recently it has become possible to also analyze more distant generations of airways.[12,18]

The intensity of remodeling in relation to the severity of asthma remains unclear and is under investigation. Wang et al,[16] using an arbitrary, 3-grade scale of the bronchial wall thickening severity (third–fifth generations), observed a gradual increase in the intensity of remodeling in subsequent degrees of asthma severity. Asthma severity grades were defined based on the severity of airflow limitation as measured by FEV1%. Mild severity of bronchial wall thickening was present in 26.7% of patients with mild asthma, 36.4% of patients with moderate asthma, and 41.5% of those with severe asthma. Moderate severity of bronchial wall thickening was present in 3.3%, 9.1%, and 26.7% of mild, moderate, and severe asthma patients, respectively. Severe bronchial wall thickening was not reported in any group of patients with asthma. It is interesting that in the study by Wang et al,[16] most patients with asthma, including those with greatest disease severerity, did not show any thickening of the bronchial walls.[16]

Berair et al[17] assessed bronchial changes in asthmatic patients with postbronchodilator FEV1% lower and higher than 80% of the predicted value, without reference to the GINA severity rating. In this formula, patients with persistent airflow limitation presented narrower mean segmental bronchial LAs and a larger mean segmental bronchial WA%. The increase in bronchial WT in patients with persistent airflow limitation was associated with a higher airway smooth muscle percentage and increased vascularity, but not with other measured markers of airway remodeling or inflammation.

In 2013, Kościuch et al[19] published a study performed in a small group of 10 patients with asthma and 12 patients with chronic obstructive pulmonary disease (COPD). The group of patients with asthma included 5 individuals with mild asthma and 5 patients with moderate asthma, classified according to the GINA recommendations. A CT scan was performed at 5 selected lung levels: superior margin of the aortic arch, tracheal bifurcation, 1 cm below the tracheal bifurcation, inferior pulmonary veins, and 2 cm above the dome of the right hemidiaphragm. The authors noted differences between the patients with mild and moderate asthma in terms of WA, total airway area, relative WT expressed as the WT to external diameter ratio, relative airway WA, internal diameter, and LA; however, these differences were not observed in COPD patients. There was also no difference in WT between the mild and moderate asthma groups.[19]

In a recent study (performed within the framework of the U-BIOPRED severe asthma study), Wilson et al[20] adopted a similar classification of patients with asthma to the one used in our study (mild-to-moderate and severe asthma groups), and also based it on the GINA recommendations. The authors assessed CT parameters and their

relationship with histological features of airway remodeling. They found no differences in the mucin or collagen quantification between all asthma groups and a group of healthy controls. The only difference was a higher median percentage of elastic fibers in the bronchial submucosa in the patients with severe asthma compared with healthy controls. Due to the low number of suitable CT images, it was not possible to compare airway morphometry data between groups.

In the present study, we focused on the relationship between the quantitative CT parameters and asthma severity according to the GINA guidelines, and not according to the degree of airflow limitation. In our previous study, we showed that the WT of all bronchial generations (third to ninth generation) is significantly greater in the asthmatic population than in healthy individuals. Other morphological features were in line with the WT. In the group of patients with asthma, WA% was significantly greater in the fourth to the ninth generation, whereas LA as well as inner diameter were significantly smaller in the seventh to the ninth generation. All these morphological features can be attributed to airway remodeling. Our observations suggest that morphotic changes are mainly noticed in the more distal bronchi.[12] Similar results were obtained in the present study. WT and WA% were greater in the groups of patients with asthma than in healthy controls, regardless of the severity of asthma and the method of patient grouping. Interestingly, in the patients with asthma, greater WT and WA% were observed only from the fourth generation of bronchi. This suggests a more distal distribution of remodeling. WT was greater in almost all distal generations in both the SA and non-SA groups, whereas WA% was consistently greater form the sixth generation onwards. Differences between the WT and WA% distribution may suggest different sensitivity of the 2 parameters in the assessment of remodeling, but the study did not address this issue. The smaller number of measurements obtained for the ninth generation limited the observation of remodeling in this generation of bronchi. Results of the current study demonstrated no differences in the parameters of airway remodeling between patients with various degrees of asthma severity according to the GINA classification. Morphological abnormalities on CT were similar in all asthma groups: mild, moderate, nonsevere (mild and moderate combined), and severe. The results are are not concurrent with those presented by Kościuch et al.[19] However, that study is limited by a small group of patients with asthma. It should also be noted that the study by Kościuch et al[19] was performed according to a scanning protocol and measurement techniques different from the ones adopted by us, and the measurements were performed only on selected axial scans. Our observations indicate that the intensity of airway remodeling is similar, regardless of the asthma severity grade. Consequently, the results suggest an early (in mild asthma) development of airway remodeling, with no noticeable progression of this process in more severe stages of the disease. The lack of differences in the intensity of airway remodeling among patients with varying degrees of the disease severity may be related to the GINA classification system of asthma severity. According to the GINA report, asthma severity is assessed retrospectively from the level of the treatment required to control the symptoms.[14] Such classification of the severity of asthma may not fully correspond to the degree of airflow limitation. Moreover, the GINA definition of asthma control is a composite end point of many variables and does not directly depend on airflow limitation. The differences in asthma severity classification may correspond to the relationship between the intensity of airway remodeling and asthma severity. Another interesting finding of our study is the lack of differences in the severity of remodeling between the groups of patients with varying degrees of airflow limitation. The study was not aimed to address this issue, which leaves space for formulating hypotheses to clarify this observation. The lack of differences in the severity of remodeling may result from the symptom- and treatment-based approach to classify asthma severity in the GINA recommendations. The severity of airflow limitation does not always correlate with the severity of symptoms and the intensity of treatment. The lack of difference in the intensity of bronchial remodeling may also be due to the similar duration of asthma in both groups. Tsurikisawa et al[21] showed that hypertrophy and hyperplasia of the airway smooth muscle, but not the reticular basement membrane, is associated with the duration of asthma. In our study, the duration of asthma in both SA and non-SA groups did not differ significantly. Another possible explanation is the occurrence of emphysema-like changes in the lung interstitium in patients with severe asthma. An emphysematous change (not analyzed in this study) may further deteriorate the airflow, independently of airway remodeling. Finally, in patients with severe asthma, remodeling of more distal airways (below the ninth generation) is possible. However, current imaging techniques do not allow for a precise imaging of the peripheral airways. Clarification of these relationships will require further research.

The present study has some limitations. First of all, it is a single-center study with relatively small groups of patients with mild-to-moderate and severe asthma. Another limitation, to some extent, is the lack of premedication with a short-acting β-2 agonist (SABA). The patients were examined during the period of good asthma control, on adequate treatment according to the GINA recommendations, but without SABA administration prior to the CT examination. A similar pattern was adopted in our other studies. The aim was to assess the status of bronchial remodeling without the impact of SABA. Such an approach corresponds most closely to the clinical condition that a patient presents in a stable period

of the disease. The obtained results raise questions that can be answered in subsequent studies carried out on larger groups of patients and based on other study protocols. This mainly concerns the relationship between the remodeling of the bronchial tree and the severity of asthma according to various criteria as well as the severity of airflow limitation and asthma phenotypes and endotypes.

In conclusion, our findings indicated a similar intensity of morphological features of airway remodeling on CT in all asthma severity groups as defined by the GINA guidelines.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

NOTE Initial results of this study were presented during an oral presentation at the European Society of Thoracic Imaging Congress in Paris (ESTI 2019). The modified abstract was published in the post-congress materials available at: https://www.myesti.org/content-esti/uploads/ESTI-Fleischner-2019-Syllabus_FINAL.pdf.

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CONTRIBUTION STATEMENT Conception and design, AO and MP; data collection, AO and MP; data analysis and interpretation, AO, MP, and UZD; statistical analysis: MP; manuscript drafting, AO and MP; funding coordination: MP. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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REFERENCES

1 Kruszewski J, Chazan R, Kuziemski K, et al. Management of asthma exacerbation in adults: guidelines for primary care doctors. Pol Arch Intern Med. 2019; 129: 842-849.

2 British Thoracic Society website. British guideline on the management of asthma. 2019; 1-208. www.brit-thoracic.org.uk. Accessed June 22, 2021.

3 Global Initiative for Asthma. Global strategy for asthma management and prevention 2021. www.ginasthma.org. Accessed June 22, 2021.

4 Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med. 1999; 160: 1001-1008.

5 Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. Am J Respir Crit Care Med. 2010; 181: 315-323.

6 Shaw DE, Sousa AR, Fowler SJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J. 2015; 46: 1308-1321.

7 Bergeron C, Al-Ramli W, Hamid Q. Remodeling in asthma. Proc Am Thorac Soc. 2009; 6: 301-305.

8 Benayoun L, Druilhe A, Dombret MC, et al. Airway structural alterations selectively associated with severe asthma. Am J Respir Crit Care Med. 2003; 167: 1360-1368.

9 Awadh N, Müller NL, Park CS, et al. Airway wall thickness in patients with near fatal asthma and control groups: assessment with high resolution computed tomographic scanning. Thorax. 1998; 53: 248-253.

10 Gono H, Fujimoto K, Kawakami S, Kubo K. Evaluation of airway wall thickness and air trapping by HRCT in asymptomatic asthma. Eur Respir J. 2003; 22: 965-971.

11 Pascual RM, Peters SP. Airway remodeling contributes to the progressive loss of lung function in asthma: an overview. J Allergy Clin Immunol. 2005; 116: 477-486.

12 Patyk M, Obojski A, Sokołowska-Dąbek D, et al. Airway wall thickness and airflow limitations in asthma assessed in quantitative computed tomography. Ther Adv Respir Dis. 2020; 14: 1-10.

13 Homer RJ, Elias JA. Consequences of long-term inflammation: airway remodeling. Clin Chest Med. 2000; 21: 331-343.

14 Global Initiative for Asthma. Global strategy for asthma management and prevention 2015. www.ginasthma.org. Accessed July 25, 2016.

15 Jiang D, Wang Z, Yu N, et al. Airway remodeling in asthma: evaluation in 5 consecutive bronchial generations by using high-resolution computed tomography. Respir Care. 2018; 63: 1399-1406.

16 Wang D, Luo J, Du W, et al. A morphologic study of the airway structure abnormalities in patients with asthma by high-resolution computed tomography. J Thorac Dis. 2016; 8: 2697-2708.

17 Berair R, Hartley R, Mistry V, et al. Associations in asthma between quantitative computed tomography and bronchial biopsy-derived airway remodelling. Eur Respir J. 2017; 49: 1601507.

18 Li Y, Dai Y-L, Yu N, Guo Y-M. Sex-related differences in bronchial parameters and pulmonary function test results in patients with chronic obstructive pulmonary disease based on three-dimensional quantitative computed tomography. J Int Med Res. 2018; 46: 135-142.

19 Kosciuch J, Krenke R, Gorska K, et al. Airway dimensions in asthma and COPD in high resolution computed tomography: can we see the difference? Respir Care. 2013; 58: 1335-1342.

20 Wilson SJ, Ward JA, Pickett HM, et al. Airway elastin is increased in severe asthma and relates to proximal wall area: histological and computed tomography findings from the U-BIOPRED severe asthma study. Clin Exp Allergy. 2021; 51: 296-304.

21 Tsurikisawa N, Oshikata C, Tsuburai T, et al. Bronchial hyperresponsiveness to histamine correlates with airway remodeling in adults with asthma. Respir Med. 2010; 104: 1271-1277.