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ASTHMA

The Effect of Inhaled Budesonide and Formoterol on Bronchial Remodeling and HRCT Features in Young Asthmatics

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Abstract Asthma is a chronic disease that may cause remodeling of the airways. We aimed to observe the effects of the combined use of inhaled budesonide and formoterol on both the reversibility of remodeling and structural changes in the airways. Thirty-six male patients (age range, 20–31) with mild-to-moderate persistent asthma were given inhaled formoterol and budesonide treatment for three months. Bronchial diameter (BD) and bronchial wall thickness (BWT), as measured by high-resolution computerized tomography, and reticular basement membrane thickness (RBMT), assessed in bronchoscopic biopsy specimens, were compared with pretreatment findings. Twenty-two age-matched male controls were also enrolled. BDs of the patients were significantly smaller than in the controls, whereas BWT and RBMT were greater. After three months BWT and RBMT of the subsegmental airways significantly decreased and BD increased. There was a prominent eosinophilic and lymphocytic infiltration in the bronchial mucosa of the asthmatics, and the eosinophilic infiltration significantly improved with treatment. Both serum total IgE and eosinophil counts were related to eosinophilic infiltration in the biopsy samples ($r = 0.494$ and $r = 0.463$, respectively). FEV_1 was positively correlated with the diameters of the segmental and subsegmental airways ($r = 0.491$ and $r = 0.265$, respectively) and negatively correlated with BWT of the subsegmental airways ($r = –0.293$) and with the RBMT of both the segmental and subsegmental airways ($r = –0.597$ and $r = –0.590$, respectively). We suggest that treatment with inhaled formoterol and budesonide may reverse increased RBMT and BWT as part of remodeling in patients with asthma.

Keywords Asthma · Airway remodeling · Formoterol · Budesonide

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Introduction

Asthma is characterized by chronic inflammation of the airways together with pathologic structural changes such as subepithelial fibrosis, increased reticular basement membrane thickness (RBMT), an increase in mucus-producing goblet cells, hyperplasia, increased mucus production from submucosal glands, angiogenesis, and an increase in smooth muscle mass. These structural changes are collectively known as airway remodeling. These changes are associated with the development of a component of irreversible airflow obstruction, which is probably the most important symptom in chronic disease and needs to be prevented [15]. Several studies have reported the reversibility of remodeling and some others have shown the persistence of these abnormalities despite treatment [4, 29, 34, 35, 37, 38, 44]. Inflammatory cell recruitment to the airways and the release of certain mediators are thought to be the major factors in the development of structural changes; local control of these factors might have some ameliorating consequences.

Recent technical advances in medical imaging have provided an opportunity to examine the airways of the lung more accurately than ever before. High-resolution

computerized tomography (HRCT) allows the visualization of airways and parenchyma in greater detail than conventional computerized tomography (CT) and plain radiography, and it has made possible the investigation of the site, magnitude, and distribution of airway abnormalities *in vivo*.

The aim of this study was to use HRCT and bronchial biopsy examinations to determine the effects of the therapeutic administration of inhaled budesonide and formoterol on the structural changes in the bronchi and RBMT, which are important components of airway remodeling.

Material and Methods

The study included 36 consecutive male patients with the diagnosis of asthma who were admitted to our department, which specifically deals with patients sent from army recruitment and training centers. The study also included 22 age-matched healthy male controls (age = 21.80 ± 1.89 and 23.09 ± 2.59 years old, respectively). The control group consisted of cases who had undergone bronchoscopy for the investigation of hemoptysis, sequel lesions, solitary pulmonary nodules, and suspicion of foreign body aspiration, and who were subsequently found to be healthy. None of the patients or controls smoked. Inclusion criteria for the study group were mild-to-moderate persistent asthma, no known major systemic illness (malignancy, diabetes mellitus, renal failure, heart failure, hematological disease, electrolyte disturbances, recent respiratory infection), and no use of systemic or inhaled steroids or any anti-asthmatic medication (except inhaled or nebulized short-acting beta-2 agonists just before transfer or admission to our institution) during the preceding six weeks. Because of the increased possible risks during bronchoscopy and the difficulties in maintaining the same standard treatment for a long period of time, severe asthma cases were excluded. Informed consent was obtained from all participants and the institutional ethical committee approved the study.

Disease stage was defined according to GINA [Global Initiative for Asthma, Global strategy for asthma management and prevention (2003), http://www.ginasthma.com]. Spirometric measurements were performed with a Minato AS-600 (Minato, Tokyo, Japan) within the first 24 h of admission and were repeated after three months. Along with routine hematologic and biochemical tests (i.e., whole blood count, erythrocyte sedimentation rate, glycemia, blood urinary nitrogen, blood lipids, serum bilurubin, gamma glutamyl transpeptidase, alkaline phosphatase, creatinine, lactate dehydrogenase, and aminotransferases), total eosinophil counts and total IgE levels (ELISA) were also obtained from the plasma. Skin prick tests, including common aeroallergens, were also performed. All patients received an in-hospital education and a brief written summary of recommendations derived from the website GINA Patient Guide website (http://www.ginasthma.com). After initial evaluation and treatment with short-acting beta agonists and inhaled steroids for 4–7 days, all patients were given prescriptions for formoterol (9 mcg) and budesonide (400 mcg), separately, for twice daily use. Patients were asked to adhere to this treatment for three months unless an attack or deterioration of their clinical situation developed; subjects who had an attack during this period were excluded. At the end of the three-month period, patients were called back to the hospital for final evaluation.

Bronchoscopy and Bronchial Biopsy

A flexible bronchoscope (Pentax FB18X, Asahi Optical, Tokyo, Japan) was used to obtain biopsy specimens from patient airways using the appropriate instrument (KW1811S forceps, Asahi Optical, Tokyo, Japan). Bronchoscopy was first performed the day before discharge, when patients were clinically stable and symptoms were relieved, and was repeated after three months of formoterol and budesonide treatment for the final evaluation. Biopsy samples were taken from the segment carina and from the most distal bifurcation visible by bronchoscopy of the subsegments, the lateral segment of the right middle lobe. The examining pathologist was blinded to the study; samples were numbered and coded by the clinician and sent to the pathology laboratory without any information regarding the treatment protocol, identity/study group of the case, or the exact site of the biopsy.

Paraffin-embedded sections (3 μm) were stained with hematoxylin and eosin to evaluate general morphology. Examination with light microscopy was performed using the oculometric method (Zeiss Axiphot Microscope, Zeiss Company, Holland). We determined the extent of leukocyte recruitment to the lung tissue by examination of the hematoxylin and eosin-stained histologic sections. A semiquantitative scoring system was used to grade the size of infiltrates, whereby + 5 signified a large (>3 cells deep) widespread infiltrate around the majority of vessels and bronchioles, and +1 signified a small number of inflammatory foci [25]. RBMT was measured with light microscopy (×400 magnification) from the line at

the end of the epithelial layer to the outer end of the lamina reticularis [45]. To do this, three consecutive sections were examined and three measurements were made at 100-μm intervals in each section; the mean of the nine measurements was recorded (Fig. 1).

Evaluation with HRCT

Bronchial diameter (BD) and bronchial wall thickness (BWT) measurements of the cases were performed by HRCT within the first 48 h of admission by a radiologist blinded to the study. The HRCT technique was performed by spiral CT (Siemens Plus 4-Power Spiral CT, Forgenheim, Germany) with a collimation of 1 mm. The window level was set to 450 Hounsfield units (HU) with a window width of 1500 HU, settings reported to be appropriate for the evaluation of BWT and bronchial lumen [19, 24]. Because lung volume might affect the wall and lumen dimensions, patients were given information and training on how to hold their breath at the end of quiet inspiration during the procedure.

An accurate definition of the inner and outer airway wall is required when performing quantitative studies of airway lumen and wall dimensions. Specifically, it is necessary to accurately identify the interface between luminal air and airway wall and between airway wall and the surrounding lung parenchyma. Measuring airway lumen and airway walls when they are not perpendicular to the scanning plane may lead to significant errors. For this reason we analyzed only structures that appeared to have been cut in cross section based on the apparent roundness of the airway lumen and having a long- to short-diameter ratio of less than 1.5.

Measurements of bronchial dimensions were performed on a computer with the use of a dedicated program (Irix v6.5 and 3-D Virtuoso V.A. 3.1, Silicon Graphics O.R., Mountain View, U.S.A.). With this method images were enlarged to 5 × and measurements were made digitally. Considering that asthma affects the lungs diffusely, measurements were performed on only the right lung and at two levels, i.e., the level of the inferior pulmonary veins (referred to here as the segmental airways) and 2 cm above the diaphragm (referred to here as the subsegmental airways). We electronically took the mean values of the measurements of three to five airways at the same level that met the above-mentioned criteria and obtained a single value for each patient (Fig. 2).

Statistical Analysis

All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL). Results were reported as mean and standard deviation (SD). For comparison of mean values, we first performed an analysis of variance then used t test (paired-samples t test to analyze pretreatment and post-treatment values of the asthmatic group, and unpaired-samples t test to compare controls with asthmatics) or the Mann-Whitney U test, as needed. Pearson correlation analysis was performed to look for the correlation between parameters. We considered $p < 0.05$ to be the level of significance.

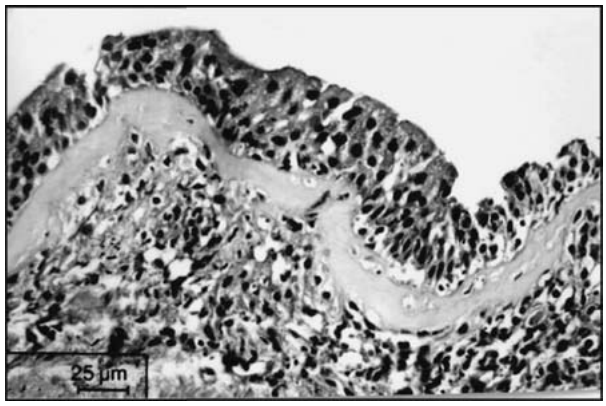

Fig. 1 Image of basement membrane obtained from an asthmatic patient

Results

Patients in the study had the diagnosis of asthma for a minimum of 1 and maximum of 15 years (mean = 5.37 ± 4.61 years). Seven patients had a positive prick test response to at least one allergen, one of whom had a low total IgE level; 17 patients had high levels of total IgE level (<120 IU/ml), and atopy could be shown in 18 patients. Spirometric measurements, total IgE, and peripheral eosinophil counts of the patients are shown in Table 1.

Table 2 compares some structural and inflammatory parameters before and after treatment. BD of the asthmatic patients as measured by HRCT was significantly smaller than in the controls in both the segmental and the subsegmental bronchi ($p = 0.056$ and $p = 0.035$, respectively). Also, BWT of the asthmatics was greater than that of the controls (the difference was significant only in the subsegmental bronchi, $p = 0.01$). Histopathologic evaluation of biopsy specimens revealed that the RBMT of the patients was significantly greater than that of the controls in both the segmental and the subsegmental airways ($p < 0.0001$ and $p < 0.0001$, respectively). In the asthmatic group, after a three-month treatment

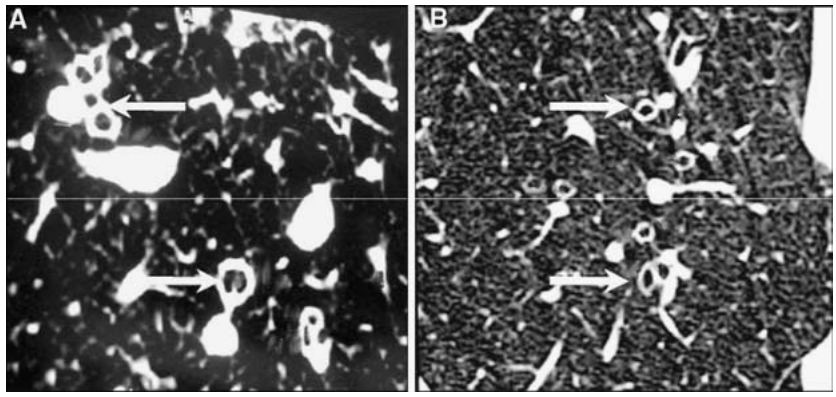

Fig. 2 Bronchial thickness in an asthmatic patient (**A**) compared with the normal image of a healthy control (**B**)

Table 1 Changes in some clinical parameters with treatment

	Before treatment	After treatment	*p* value
Total IgE (IU/ml)	551.28 ± 581.92	385.34 ± 492.84	0.024
Eosinophil count (cells/ml)	198.80 ± 88.90	153.57 ± 34.71	0.022
FEV_1 (% predicted	70.72 ± 7.37	75.97 ± 6.85	0.0.0001
FVC (% predicted)	71.86 ± 10.41	76.75 ± 7.90	0.0001
FEF (% predicted)	59.16 ± 14.79	66.44 ± 14.51	0.003

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; FEF = forced expiratory flow

Table 2 Comparison of gross structural and histopathological changes before and after treatment

Parameter	Mean control data	Asthma before treatment	Asthma after treatment	*p* value*
Segmental airways				
Mean BWT (mm)	1.38 ± 0.13	1.39 ± 0.24	1.36 ± 0.26	NS
Mean BD (mm)	3.56 ± 0.60	3.09 ± 0.90	3.06 ± 0.86	NS
Mean RBMT (μm)	5.47 ± 1.74	10.05 ± 2.62	9.41 ± 2.36	0.083
Eosinophilic infiltration score[a]	1.17 ± 0.39	2.00 ± 1.06	1.33 ± 0.61	0.003
Lymphocyte infiltration score[a]	1.19 ± 0.40	1.41 ± 0.64	1.22 ± 0.42	0.071
Subsegmental airways				
Mean BWT (mm)	0.89 ± 0.19	1.03 ± 0.21	0.86 ± 0.23	<0.0001
Mean BD (mm)	1.63 ± 0.28	1.45 ± 0.39	1.62 ± 0.32	<0.0001
Mean RBMT (μm)	4.90 ± 1.37	8.57 ± 1.70	7.88 ± 1.76	0.017
Eosinophilic infiltration score[a]	1.16 ± 0.38	2.06 ± 1.22	1.20 ± 0.41	0.004
Lymphocyte infiltration score[a]	1.14 ± 0.35	1.52 ± 0.81	1.33 ± 0.58	0.09

BWT = bronchial wall thickness measured by HRCT in mm; BD = bronchial diameter measured by HRCT in mm; RBMT = reticular basement membrane thickness measured histopathologically in μm

[a] Term described in the Materials and Method section

*Asthma before treatment vs. asthma after treatment, paired-samples *t* test

BWT and RBMT of the subsegmental airways significantly decreased and BD increased but these changes were not significant in the segmental airways. Post-treatment RBMT was still greater in the patient group than in the controls (in segmental bronchi $p < 0.0001$, and in subsegmental bronchi $p < 0.0001$).

The lymphocytic and eosinophilic infiltration scores of bronchial mucosa were significantly higher in the patients than in the controls (in segmental bronchi $p = 0.11$ and $p < 0.01$, respectively, and in subsegmental bronchi $p < 0.05$ and $p < 0.005$, respectively). In the asthmatic group, the eosinophilic infiltration score significantly improved with treatment in both the segmental and the subsegmental airways (Table 2), but it was still higher than in the controls ($p = 0.042$). Except for two cases from the patient group and one patient from the control group, there was no polymorphonuclear leukocyte infiltration in the biopsy specimens; therefore, these results were not studied statistically and are not shown in Table 2.

We did not find a correlation between dimensional measurements by HRCT and histopathologic measurements of RBMT. In the patient group, as would be expected, FEV_1 was positively correlated with the

diameters of the segmental and subsegmental airways ($p = 0.0001$, $r = 0.491$ and $p = 0.045$, $r = 0.265$, respectively) and negatively correlated with airway wall thickness of the subsegmental airways ($p = 0.026$, $r = –0.293$), as depicted in Figure 3. In addition, FEV_1 was negatively correlated with the RBMT of both the segmental and the subsegmental airways ($p < 0.001$, $r = –0.597$ and $p < 0.001$, $r = –0.590$). Regarding the histopathologic examination of leukocyte infiltration, lymphocytic and eosinophilic infiltration scores showed a good correlation with each other ($p = 0.001$, $r = 0.580$). Our findings did not show a relationship between lymphocytic infiltration scores and gross structural or RBMT measurements, but eosinophilic infiltration scores were weakly correlated with RBMT of the segmental and subsegmental airways ($p = 0.028$, $r = 0.366$ and $p = 0.058$, $r = 0.297$) in the asthmatic group. Moreover, both total serum IgE and eosinophil counts were related to eosinophilic infiltration scores in the biopsy samples of the patients ($p < 0.001$, $r = 0.494$ and $p = 0.003$, $r = 0.463$, respectively).

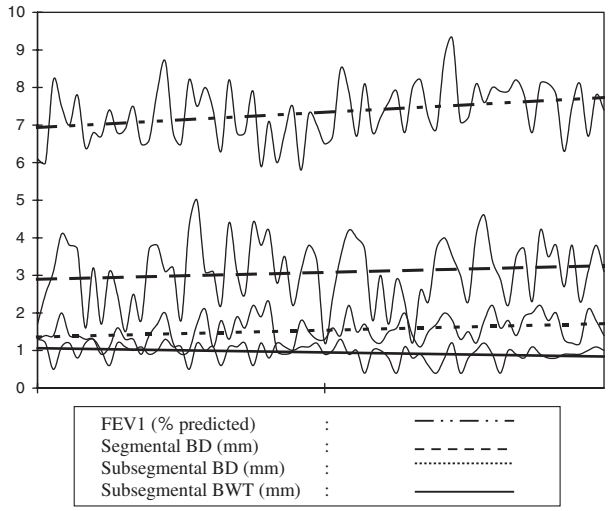

Fig. 3 In asthmatic patients FEV_1 was positively correlated with segmental bronchial diameter (BD) and subsegmental BD and negatively correlated with subsegmental bronchial wall thickness (BWT). First half of the category axis shows pretreatment values and the second half shows post-treatment values of the patients. FEV_1 is represented at one tenth of the actual value

Discussion

The current concept of asthma is that chronic inflammation results in variable airflow limitation and increased airway responsiveness, which manifests as symptoms of wheezing, chest tightness, coughing, and dyspnea (GINA, http://www.ginasthma.com). The extent of bronchial mucosal inflammation may determine the severity of disease [10, 20, 26]. Although inflammation is associated with injury and airways remodeling is related to the severity of disease [7], remodeling of the bronchial mucosa can be present even in children and in asymptomatic and mild asthma patients [3, 22, 23]. Prevention of and/or reversing the structural changes, namely, remodeling of the airways, may be the most important step in avoiding the irreversible component of impaired lung function. Because remodeling is thought to be the result of injurious events taking place in the bronchi, which are apparently related to both inappropriate treatment and clinical management, one might suggest that at least some part of these events should be evitable. It is possible that a significant proportion of asthmatic patients are undertreated and early intervention may prevent progression to a more severe disease state. Guidelines allow for the stepping-up or the stepping-down of therapy; however, there is evidence to suggest that the stepped approach to treatment is not followed in general practice. In a large-scale study, 4733 patients were at step 1 (of whom 55.4% should have been at step 2) and 8106 patients were at step 2 (of whom 54.6% should have been stepped-up) [31]. Possibly, increment in RBMT and/or other accompanying structural changes might be indicators of treatment efficacy or requirements in some cases.

Airway pathology and the degree of remodeling can be assessed using a number of methods other than the measurement of RBMT, such as the demonstration of increased deposition of collagen and connective tissue proteins and smooth muscle abnormalities; however, most of these other methods are costly and technically difficult. On the other hand, measurement of RBMT is relatively standardized, practical, and quantitative. The reticular basement membrane is a well-defined band beneath the bronchial epithelium that can be measured and reported objectively (Fig. 1). In normal subjects, the range of reported values of RBMT is 3.2–8.4 μm [17, 45]. It has been demonstrated that RBMT, assessed by endobronchial biopsy, was correlated with the percentage of smooth muscle, with submucosal mucous gland, with inner-wall area in large cartilaginous airways, and with inner wall area and area of smooth muscle in small cartilaginous airways [16]. However, bronchoscopy is an invasive method that causes discomfort, whereas assessment of the peripheral small airways and of changes in the deep submucosal tissue and airway smooth muscle in large airways is technically difficult. HRCT scanning accurately reflects the anatomical and physiologic changes in the

airways and lung parenchymal tissues and has been proven to be the optimal noninvasive modality for patients with asthma [18]. Nakano et al. [30] reviewed studies on the use of HRCT in the assessment of airway remodeling and concluded that it was a valuable tool for the study of airway disease. We decided to use both methods to investigate different aspects of remodeling.

The combination of a long-acting beta-2 agonist and an inhaled corticosteroid is more efficacious in treating asthma than other combination therapies or either therapy alone. This is because of the complementary and synergistic interactions between corticosteroids and long-acting beta-agonists. Both systemic and inhaled corticosteroids have been shown to reverse beta-2 receptor downregulation [12]. Corticosteroids also reportedly modulate the efficiency of coupling between beta-2 receptors and the adenylate cyclase system [28]. Another study has shown that proinflammatory cytokines such as interleukin-1 beta, and transforming growth factor beta-1 regulate the coupling of beta-2 receptors to adenylate cyclase and receptor sensitivity. Corticosteroids may prevent and even reverse these effects by reducing the concentration of such cytokines [21]. On the other hand, long-acting beta-2 agonists prime the glucocorticoid receptors for subsequent corticosteroid binding [1]. Other studies have shown that translocation of the glucocorticoid receptor from the cell cytosol to the nucleus is increased by long-acting beta-agonists [9, 39]. As a single agent, formoterol has been reported to reduce the number of airway eosinophils in the airway biopsies of asthmatic patients, but this effect was demonstrated only in subjects with high baseline numbers of eosinophils [42]; however, Overbeek et al. [33] reported that formoterol added to low-dose budesonide had no additional anti-inflammatory effect in asthmatic patients.

Inhaled corticosteroids are the mainstay of asthma therapy and are currently the most effective way to control inflammation, particularly of the eosinophilic type [8]. It has been demonstrated that therapeutic administration of budesonide decreased peribronchiolar extracellular matrix deposition, reduced inflammatory mediator production, and modulated transforming growth factor beta signaling pathways, which in turn ameliorated allergen-induced airway remodeling [29]. Another study showed that the use of low doses of inhaled corticosteroids for four weeks resulted in the resolution of eosinophilic infiltration and the downregulation of remodeling markers like metalloproteinase-9 and tissue inhibitor metalloproteinase-1 in persistent-mild asthma [41]. However, there is also evidence to suggest that many of these inflammatory cells remain elevated despite treatment with corticosteroids [26]. We did not study the mediators mentioned above but showed that there was prominent lymphocytic and eosinophilic infiltration of bronchial mucosa, which improved after treatment. Further work is clearly needed in this area.

Reversibility of increased RBMT has always been an issue of debate. Lundgren et al. [27] and Boulet et al. [4] reported no change in RBMT following either long- or short-term (4 months to 10 years) use of inhaled corticosteroids; however, in other studies treatment with inhaled corticosteroids lasting 6 weeks, 4 months, or 6 months resulted in a modest decrease in RBMT [14, 32, 38]. Hoshino et al. [13] showed that after six months of treatment with inhaled beclomethasone dipropionate (400 mcg twice a day) resulted in a significant decrease in the thickness of the lamina reticularis of the epithelial basement membrane and in the number of activated eosinophils, T lymphocytes, and fibroblasts. Ward et al. [44] evaluated the effects of up to 12 months of treatment with high-dose (1.5 mg/day) fluticasone propionate. Following three months of treatment, inflammatory cell counts in the biopsy samples fell significantly, with no further effect on inflammation with up to 12 months of treatment. These changes in airway inflammation preceded a normalizing effect on RBMT, which was observed in biopsies obtained at 12 months [44]. Sont et al. [37] conducted a prospective, randomized, single-blinded trial with a two-year followup. They initially obtained bronchial biopsies from 75 adults with mild-to-moderate asthma and after two years found that vigorous treatment with corticosteroids, inhaled steroid equivalent to 800 mcg/day of budesonide, resulted in reduced RBMT [37]. We also showed that RBMT, which was initially and finally thicker in asthmatic patients than in controls, was reduced with treatment in patients without a documented attack within the previous three months. Together, these findings have led to the hypothesis that inhaled corticosteroids might be effective in reducing RBMT when used for a long period of time and at a high dose. Meanwhile, Ward and Walters [43] recently reviewed the literature to bring together recent findings about the effects of corticosteroid medication on airway remodeling in asthma. They concluded that the effects of corticosteroids on airway remodeling vary a great deal; some aspects are steroid-responsive, while others are not or are less so. It is possible that different manifestations of remodeling require different doses and time scales for treatment to be effective.

Paganin et al. [34] considered bronchial wall thickening in asthmatic patients as an irreversible

structural abnormality, although bronchial wall thickening has also been described as being reversible [5]. The reversibility of remodeled airways is supported in part by a pathologic study that showed that subepithelial collagen deposition, which is one component of bronchial wall thickening, was reduced significantly in asthmatic patients who had undergone intensive anti-inflammatory therapy [14]. In addition, airway wall thickness measured by HRCT in patients with asthma has been demonstrated to correlate with the severity of asthma [2, 11, 24]. Vignola et al. [40] reported that sputum elastase, metalloproteinase-9, and tissue-inhibitor metalloproteinase-1 are related and reflect the extent of structural changes of the airways, as assessed by HRCT. In a new study, BWT was evaluated by HRCT in patients with asthma; the results indicated that airway structural abnormalities were associated with the severity of asthma and these abnormalities were, at least partially, reversible after the successful control of asthma symptoms [24]. As explained in the Results section, our cases with mild-to-moderate persistent asthma also presented with HRCT and histopathologic findings of remodeling. In general, BWT decreased while bronchial diameter increased with treatment, but this finding was significant only in the subsegmental airways.

We found that FEV_1 was positively correlated with the diameters of the segmental and subsegmental airways and negatively correlated with airway wall thickness of the subsegmental airways. Furthermore, FEV_1 was negatively correlated with the RBMT of the segmental and subsegmental airways. Improvement in lung function associated with reduced RBMT during treatment with corticosteroids was reported in some [37] but not all studies [4].

Some studies have indicated that IgE levels may not be a reliable indicator of disease severity and that the frequency and severity of IgE-related exacerbations may be independent of the underlying disease and are influenced by other extrinsic factors [36]. Meanwhile, it has been reported that peripheral blood eosinophilia and bronchial wall thickening seen on HRCT were significantly and independently associated with persistent airflow obstruction [6]. We did not find a relationship between total serum IgE levels and eosinophil counts with spirometric functions and structural measurements, but both were related to eosinophilic infiltration scores in the biopsy samples.

We evaluated only a few aspects of airway remodeling; there might be other reversible and irreversible components. However, after a three-month treatment of inhaled budesonide and formoterol, along with other control measures, the final outcome is highly likely to represent structural changes resistive to treatment. We conclude that treatment with inhaled formoterol and budesonide, for a long enough period of time, may at least partially reverse increased RBMT and BWT as a part of remodeling in patients with mild-to-moderate persistent asthma. Defining the reversible and irreversible components of airway remodeling and its clinical implications warrants further investigation.

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