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Clinical Trial Paper

Bronchial wall thickening is associated with severity of chronic rhinosinusitis

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ABSTRACT

Background: Though the relationship between chronic rhinosinusitis (CRS) and lower airway diseases is well recognized, the impact of CRS on bronchial wall structure has not been elucidated. Here, we evaluated the bronchial wall structure of CRS patients with or without diagnosed airway diseases by three-dimensional computed tomography (3D-CT).

Methods: Subjects who underwent both chest CT and sinus CT within a year were recruited from consecutive medical records. CRS was defined as a Lund-Mackay score (LMS) of over 5 points. Airway dimensions were measured using validated software. Standard blood tests and pulmonary function tests were performed, and their correlation with airway thickness was examined.

Results: One-hundred-seventy-two patients were recruited (93 CRS subjects and 79 non-CRS subjects). The bronchial walls of CRS subjects were significantly thicker than those of non-CRS subjects. CRS and asthma were related to bronchial wall thickening by multivariate linear regression analysis adjusted for age, smoking status, and chest symptoms. In addition, LMS was significantly correlated with bronchial wall thickening.

Conclusion: Airway walls in CRS subjects were thicker than those in non-CRS subjects and associated with the severity of CRS. These data indicate strong relationship between upper and lower airways regardless of chest symptoms or diagnosed airway diseases.

1. Introduction

The relationship between upper and lower airway diseases is widely recognized as the concept of "united airway disease" [1–3]. Indeed, nasal mucosa and bronchial mucosa have similar structures (e.g., epithelial cells, goblet cells) and function (e.g., mucociliary clearance). Furthermore, both upper and lower airway diseases have common risk factors, such as smoking, pollutants, or exposure to cold dry air.

The co-existence of chronic rhinosinusitis (CRS) and lower airway diseases has long been observed by clinicians. In addition, under the concept of "united airway disease", there is increasing evidence of the association between CRS and lower airway diseases such as bronchial asthma [4,5], chronic obstructive pulmonary disease (COPD) [4,6], and bronchiectasis [7,8]. In asthmatic patients, CRS is considered one of the common comorbidities and is related to disease severity and/or eosinophilic inflammation [9–11]. The high prevalence of CRS among COPD patients was also reported by several groups [6]. Sixty-two percent of bronchiectasis patients have CRS, and CRS is related to disease severity and poor health-related quality of life in those patients [7]. In addition, it is reported that CRS patients, regardless of their lung diseases, have a greater deficit on pulmonary function tests than healthy subjects [12,13].

Quantitative assessment of airway dimensions by three-dimensional computed tomography (3D-CT) is well established as a method of

Abbreviations: CRS, chronic rhinosinusitis; CT, computed tomography; LMS, Lund-Mackay score.

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analyzing bronchial wall structure in lower airway diseases. In previous reports, airway dimensions correlated strongly with pulmonary function in asthma [14,15] and COPD [16,17]. Furthermore, bronchial wall thickness as assessed by 3D-CT was reduced after treatment with inhaled corticosteroid plus a bronchodilator [18] or bronchial thermoplasty [19,20] in asthmatic patients. These observations imply the usefulness of 3D-CT for evaluating airway diseases comprehensively, but there are few studies assessing airway dimensions in non-pulmonary diseases including CRS.

The aim of this study was to investigate the relationship between CRS and bronchial structure by quantifying using 3D-CT. To evaluate the impact of CRS on the lower airway in symptomatic and asymptomatic patients, we performed a retrospective medical record-based study and consecutively analyzed CT data taken for various reasons in our hospital. CRS was diagnosed using a sinus CT scoring system. The data from blood and pulmonary function tests were collected and analyzed together with airway dimensions.

2. Materials and methods

2.1. Subjects

Patients who underwent both chest CT and sinus CT within one year from January 2011 to May 2016 were consecutively recruited from medical records at Nagoya University Hospital. Subjects with acute pneumonia, interstitial lung disease, bronchiectasis, lung resection, acute rhinosinusitis, or nasal fracture were excluded. The ethics committee of Nagoya University Hospital approved this retrospective cross-sectional study (number: 2016–0110) and waived the requirement for informed consent.

2.2. Sinus CT data acquisition and analysis

Sinus CT images were obtained using a 16-row or 64-row multi-detector CT scanner (Aquilion; Toshiba Medical, Tokyo, Japan). Two otolaryngologists (M.T. and N·N.) who were blinded to the subject's information separately evaluated and scored CT images according to the Lund-Mackay score (LMS) [21]. A score of 0, 1, or 2 was assigned to each sinus region (maxillary, anterior/posterior ethmoidal, sphenoidal, and frontal) and a score of 0 or 2 was assigned for each ostiomeatal complex to give a possible score of up to 24. The intraclass correlation coefficient (ICC), which evaluated interobserver reliability, was 0.966 ($p < 0.01$). CRS was defined as over 5 LMS points, and non-CRS was defined as under 5 LMS points according to previous reports [11,22,23].

2.3. Chest CT data acquisition and analysis

Chest CT images were obtained using a 16-row or 64-row multi-detector CT scanner (Aquilion; Toshiba Medical, Tokyo, Japan). The scans were obtained during a breath-hold at inspiration using the following scan parameters: X-ray tube voltage of 120 kVp; automatic tube-current; gantry rotation speed of 0.5 s; and beam collimation of 16 × 1 mm or 64 × 0.5 mm. Axial thin-section CT images for 3D-CT were reconstructed as 0.5–1.0 mm thick slices using a high spatial-frequency reconstruction algorithm. The DICOM data for 3D-CT were transferred to a commercial 3D workstation (Synapse Vincent version 4.3; Fujifilm Medical Systems, Tokyo, Japan). After the chest 3D-CT DICOM data were read, trachea or bronchi from extracted at each side of the lung, and a tracheobronchial tree was reconstructed automatically. We identified the upper apical segmental bronchus B^1) and posterior basal segmental bronchi (B^{10}) in the right lung. After each bronchus point was selected on the axial image, three generations (third to fifth) on both the rightB^1 and B^{10} were measured in all subjects. Measurement of airway dimensions was performed semi-automatically by the workstation as wall thickness percentage (WT%), wall area percentage (WA%), luminal area/body surface area (Al/BSA, mm^2/m^2), and wall area/body surface area (WA/BSA, mm^2/m^2), which were measured with the full-width at half-maximum method [24,25] (Fig. S1). Intraobserver error was tested with one observer (S.M.) measuring airway dimensions for the same bronchi in 30 randomly selected subjects twice at a one-month interval. To evaluate interobserver error, another observer (S·I.) independently measured the same indexes of three generations on the right B^1 and B^{10} bronchi in all subjects. Intraobserver and interobserver reliability were calculated with the ICC. The ICC of intraobserver was 0.99 ($p < 0.01$), and the ICC of interobserver was 0.92 ($p < 0.01$), respectively.

2.4. Clinical examinations

Spirometry was performed with a calibrated dry spirometer, a FUDAC-77 (Fukuda Denshi Co., Ltd., Tokyo, Japan), according to the American Thoracic Society (ATS) standards applied in our hospital. Spirometry data within 3 months after subjects underwent chest CT was selected. Blood data were also selected by same method.

2.5. Statistical analysis

All statistical analyses were performed with PASW Statistics version 24.0 (SPSS, Inc, Chicago, IL, USA). Data were expressed as mean ± standard deviation (SD). Differences of categorical variables between groups were analyzed by chi-square test. Differences of continuous variables between two groups were analyzed by unpaired *t*-test. Linear regression analysis and Pearson's rank correlation analysis were used to estimate the relationship between airway dimensions and clinical parameters. Multivariate regression analyses with airway dimensions as the independent variable were performed to evaluate the relative contributions of clinical parameters. Differences were considered significant if P values were less than 0.05.

3. Results

3.1. Characteristics

Of 312 subjects, 89 were excluded for significant abnormal findings on chest CT (n = 83), acute rhinosinusitis (n = 3), lung resection (n = 2), or nasal fracture (n = 1). Forty-one subjects without thin-slice CT (≤1 mm) were also excluded. One-hundred-seventy-two subjects were eligible and recruited. Seventy-nine subjects were categorized as non-CRS, and 93 subjects were categorized as CRS (Fig. 1). The most common reason for performing sinus CT was CRS screening (67%, n = 122), whereas there were various reasons for taking chest CT, such as screening or evaluation of lung diseases (35.5%, n = 61), malignancy (16.9%, n = 29), or connective tissue disease (14.5%, n = 25) (Table 1).

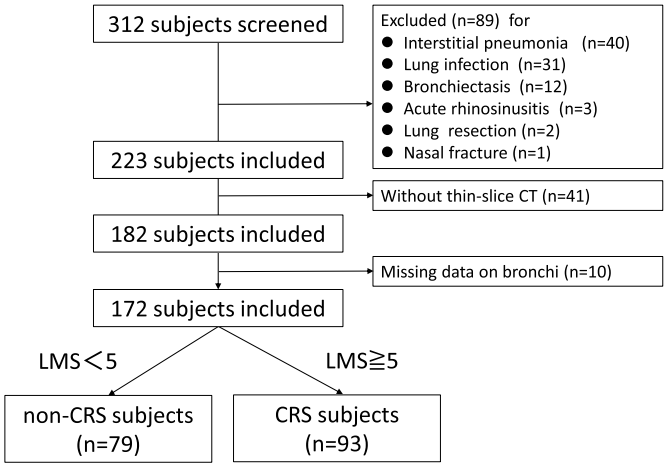

Fig. 1. Patient flow diagram.
LMS, Lund-Mackay score; CRS, chronic rhinosinusitis.

Table 1
Reasons for CT scanning.

(A) Reasons for sinus CT	n	%
Diagnosis of sinus disease	110	64
Cancer screening	22	12.8
Nasal bleeding/injury	9	5.2
Other reasons[a]	31	18

(B) Reasons for chest CT	n	%
Chest symptoms[b]/diagnosed lung disease[c]	61	35.5
Cancer screening	29	16.9
Screening for connective tissue disease	25	14.5
Other reasons[d]	57	33.1

[a] Other reasons included connective tissue disease (n = 14), sleep apnea syndrome (n = 6), health screening (n = 5), transplant screening (n = 4), and fever screening (n = 3).
[b] Chest symptoms included chest pain/back pain (n = 9), bloody phlegm (n = 7), cough (n = 5), or dyspnea (n = 2).
[c] Diagnosed lung diseases included asthma (n = 29) or COPD (n = 9).
[d] Other reasons included health screening (n = 27), cardiovascular disease screening (n = 18), screening before starting biological therapy (n = 4), transplant screening (n = 4), or fever screening (n = 4).

Baseline characteristics are listed in Table 2. CRS subjects included a higher percentage of male patients and had higher blood eosinophil counts than non-CRS subjects ($p < 0.05$). There were no significant differences in age, smoking status, ratio of comorbidity, medication, or pulmonary function tests between the two groups.

3.2. Airway dimensions and chronic rhinosinusitis

Bronchial wall thickness as WT% and WA% values of 4th and 5th generation bronchi at B1 and B10 in CRS subjects were significantly larger than those in non-CRS subjects (Table 3). In addition, the airway luminal areas (AI/BSA) of B^1 4th generation and B^{10} 5th generation in CRS subjects were smaller than those in non-CRS subjects. However, airway dimensions of proximal bronchi (3rd generation bronchi) were not significantly different between the two groups.

3.3. Univariate and multivariate regression analysis of airway dimensions

Univariate linear regression analysis showed that CRS and asthma were related to bronchial wall thickness. After adjusting for age, smoking status, chest symptoms, and asthma, the simultaneous multivariate linear regression analysis for bronchial wall thicknesses of 4th and 5th generation bronchi retained CRS as an independent variable. In addition, CRS was correlated with luminal narrowing of 4th or 5th generation bronchi by multivariate linear regression analysis (Table 4). Asthma was correlated with bronchial wall thickness and luminal narrowing at some bronchi by multivariate linear regression analysis adjusted for age, smoking status, and chest symptoms (Table S1).

3.4. Relationship between airway dimensions and clinical parameters

Relationships between bronchial wall thickness and various clinical parameters in all subjects are shown in Fig. 2 and Table 5. There was a significant positive association between wall thickness and LMS, and significant negative associations between wall thickness and percent of forced expiratory volume in 1-s ($FEV_{1.0}$) predicted value. In addition, there was a positive correlation between wall thickness and blood eosinophil counts, whereas there were no significant correlations between wall thickness and smoking status, blood WBC counts, blood neutrophil counts, or CRP levels in serum. Moreover, these observations were also found in the patient group taken chest CT for reasons other than chest symptoms/diagnosed lung disease (Table 1, n = 111),

Table 2
Characteristics.

	Variable	All subjects (n = 172)	Non-CRS (n = 79)	CRS (n = 93)	*P* value
	Male sex, n (%)	86 (50)	31 (39.2)	55 (59.1)	0.01
	Age (y)	60.7 ± 14.7	59.8 ± 15.0	61.4 ± 14.4	0.48
	Pack-years of smoking[a]	14 ± 24.6	12.5 ± 22.0	15.3 ± 26.6	0.49
	LMS	5.5 ± 5.0	1.2 ± 1.5	9.1 ± 3.8	<0.01
Comorbidity, n (%)					
	Asthma	29 (16.8)	10 (12.7)	19 (20.4)	0.22
	COPD	9 (5.2)	4 (5.1)	5 (5.4)	0.93
	Malignancy	22 (12.7)	9 (11.4)	13 (14.0)	0.65
	CTD	32 (18.6)	18 (22.8)	14 (15.8)	0.24
	Hematologic disease	24 (13.9)	10 (12.7)	14 (15.1)	0.83
	Others	26 (15.1)	10 (12.7)	16 (17.2)	0.52
Drugs, n (%)					
	PSL	36 (20.9)	20 (25.3)	16 (17.2)	0.25
	ICS, ICS/LABA	20 (11.6)	8 (10.1)	12 (12.9)	0.63
	Macrolide	6 (3.4)	2 (2.5)	4 (4.3)	0.68
	Nasal corticosteroid	16 (9.3)	5 (6.3)	11 (11.8)	0.29
Lung function[a]					
	FEV_1 (L)	2.4 ± 0.8	2.4 ± 0.7	2.4 ± 0.8	0.74
	FEV_1 predicted value (%)	97.2 ± 19.5	94.9 ± 19.2	99 ± 19.6	0.24
	FEV_1/FVC (%)	74.3 ± 9.8	75.6 ± 8.6	73.4 ± 10.5	0.21
Blood sample					
	WBC (/μL)[b]	6144 ± 2422	5960 ± 1957	6298 ± 2755	0.36
	Neutrophils (/μL)[b]	3390 ± 1423	3409 ± 1483	3393 ± 1410	0.94
	Eosinophils (/μL)[c]	192 ± 217	127 ± 140	255 ± 257	<0.01
	CRP (mg/dl)[c]	0.26 ± 0.67	0.21 ± 0.52	0.3 ± 0.76	0.48

P values were tested by unpaired *t*-test, which are presented as means ± SD, or chi-square test, which were presented as n (%) between non-CRS subjects and CRS subjects.
LMS, Lund-Mackay score; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; PSL, prednisolone; ICS, inhaled corticosteroid; LABA, long-acting β-receptor antagonist; $FEV_{1.0}$, forced expiratory volume in 1 s; FVC, forced vital capacity; WBC, white blood cell; CRP, C-reactive protein.
[†]Lung functions were evaluated in all subjects (n = 127), non-CRS subjects (n = 54), and CRS subjects (n = 73).
[a] Pack-years of smoking was evaluated in all subjects (n = 150), non-CRS subjects (n = 67), and CRS subjects (n = 83).
[b] WBC and neutrophils were evaluated in all subjects (n = 162), non-CRS subjects (n = 74), and CRS subjects (n = 88).
[c] Eosinophils and CRP were evaluated in all subjects (n = 129), non-CRS subjects (n = 64), and CRS subjects (n = 65).

Table 3
Airway dimension in all subjects.

			non-CRS (n = 79)	CRS (n = 93)	*P* value
B^1	3rd	WT (%)	36.1 ± 4.9	36.8 ± 5.6	0.38
		WA/BSA (mm^2/m^2)	15.8 ± 4.4	15.9 ± 7.7	0.94
		Al/BSA (mm^2/m^2)	11.5 ± 4.6	10.8 ± 4.3	0.32
		WA (%)	58.7 ± 6.2	59.5 ± 7.1	0.42
	4th	**WT (%)**	35.6 ± 4.4	38.5 ± 4.1	< **0.01**
		WA/BSA (mm^2/m^2)	9.2 ± 3.3	9.4 ± 3.1	0.63
		Al/BSA (mm^2/m^2)	7.0 ± 3.6	6.0 ± 2.5	**0.04**
		WA (%)	57.9 ± 5.5	61.7 ± 5.0	< **0.01**
	5th	**WT (%)**	37.3 ± 6.2	40.6 ± 5.4	< **0.01**
		WA/BSA (mm^2/m^2)	6.0 ± 2.3	6.6 ± 2.4	0.06
		Al/BSA (mm^2/m^2)	4.1 ± 2.2	6.6 ± 2.4	0.08
		WA (%)	59.9 ± 6.0	64.3 ± 6.2	< **0.01**
B^{10}	3rd	WT (%)	34.3 ± 5.2	35.0 ± 6.8	0.49
		WA/BSA (mm^2/m^2)	16.3 ± 3.3	15.5 ± 3.3	0.14
		Al/BSA (mm^2/m^2)	13.1 ± 4.9	12.3 ± 4.9	0.32
		WA (%)	56.3 ± 6.9	57.0 ± 8.8	0.57
	4th	**WT (%)**	33.5 ± 4.7	36.8 ± 5.7	< **0.01**
		WA/BSA (mm^2/m^2)	11.9 ± 3.7	12.8 ± 3.4	0.11
		Al/BSA (mm^2/m^2)	10.0 ± 4.0	9.2 ± 4.1	0.23
		WA (%)	55.3 ± 6.2	59.5 ± 7.0	< **0.01**
	5th	**WT (%)**	34.2 ± 4.1	38.8 ± 5.2	< **0.01**
		WA/BSA (mm^2/m^2)	9.6 ± 3.1	9.8 ± 3.2	0.65
		Al/BSA (mm^2/m^2)	7.7 ± 3.6	6.2 ± 2.9	< **0.01**
		WA (%)	56.3 ± 5.4	62.0 ± 6.2	< **0.01**

Data are presented as mean ± SD. *P* values were tested by the unpaired *t*-test. WT, airway wall thickness; WA, airway wall area; Al, airway luminal area; BSA, body surface area.

although the correlation coefficients were smaller (Table S2, Table S3).

4. Discussion

In this study, we demonstrated that CRS patients have bronchial wall thickening and luminal narrowing compared to non-CRS patients. In addition, multivariate regression analysis showed that CRS was correlated with bronchial wall thickness and luminal narrowing of the 4th and 5th generations after adjusting for age, smoking status, chest symptoms, and asthma. These observations suggest a strong relationship between CRS and bronchial structural changes as evaluated by 3D-CT. Furthermore, we observed a positive correlation between LMS and airway wall thickening. LMS is a well-established CT-based scoring system that quantifies the mucosal thickening and fluid levels of sinus cavities and is related to the endoscopy score and increasing grade of polyposis in CRS [22,26]. Thus, we concluded that bronchial wall thickening was associated with the severity of CRS. To the best of our knowledge, this is the first report regarding CRS and bronchial wall thickness evaluated by 3D-CT. Moreover, in this study, we consecutively examined all patients who have undergone sinus CT and chest CT in our hospital, regardless of symptoms or diagnosed airway diseases. From this point of view, our observations imply the impact of CRS on lower airways of with and without prevalent airway diseases.

The assessment of airway dimensions by CT is a noninvasive and widely used as a surrogate for evaluation of airway wall remodeling. In COPD patients, bronchial wall thickening is related to low pulmonary function [16,17], high St George's Respiratory Questionnaire (SGRQ) scores [27], and high mortality from exacerbations [28]. In asthmatic patients, airway wall thickening is associated with airway obstruction [15], disease severity [14], fraction of exhaled nitric oxide value [29], and disease duration [14]. Inhaled budesonide and formoterol therapy reduce bronchial wall thickness as measured by high-resolution CT as well as reticular basement membrane thickness as evaluated by histopathological samples in asthmatic patients [18]. Bronchial thermoplasty improves airway wall thickening as measured by 3D-CT as well as the Asthma Quality of Life Questionnaire (AQLQ) score [19,20]. Furthermore, recent large longitudinal cohort studies revealed that airway wall thickening at enrollment was associated with a greater FEV_1 decline and increased incidence of COPD after 3–6 years [30,31], though most participants did not have lung diseases at the first visit of these studies. Charbonnier et al. showed that smoking increased airway wall thickness and smoking cessation decreased it during a 5-year follow-up [32]. Taken together with these findings, quantitative CT analysis of airway dimensions is a useful technique for assessing not only the severity of airway diseases but also subclinical airway inflammation.

Univariate regression analysis showed that airway dimensions had significant associations with CRS and asthma. Several reports described bronchial wall thickening in asthmatic patients [14,15,29], and our result is consistent with those findings. In addition, the numbers of eosinophils in the blood showed a positive correlation with WA% at B10. CRS is a major comorbidity of asthma and related to disease severity. Indeed, the severity of CRS evaluated by LMS using sinus CT is correlated to lower lung function as well as eosinophilic inflammation in asthma [11,33]. The ratio of coexistent asthma is higher in eosinophilic CRS patients than that in non-eosinophilic CRS patients [34]. Furthermore, the similarities of histopathological changes based on type 2 inflammation between CRS and asthma are well documented [35–37]. However, after adjusting for confounding factors including asthma, the simultaneous multivariate linear regression analysis for bronchial wall thickness retained CRS as an independent variable. Because all subjects were not evaluated by pulmonologists, we cannot deny the possibility of underdiagnosed asthma. However, we may conclude that CRS subjects who are not recognized as having asthma in the real world show

Table 4
CRS is associated with airway dimensions by univariate and multivariate regression analysis.

		Univariate			Multivariate		
		Estimate	95% CI	**P* value	Estimate	95% CI	*†P* value
B^1	3rd Al/BSA	−0.07	−2.01, 0.66	0.319	−0.07	−2.22, 0.8	0.35
	3rd WA%	0.06	−1.2, 2.83	0.43	0.03	−2, 2.97	0.7
	4th Al/BSA	−0.15	−1.87, −0.02	0.04	−0.18	−2.05, −0.13	**0.03**
	4th WA%	0.34	2.23, 5.41	<0.01	0.29	1.52, 5.35	< **0.01**
	5th Al/BSA	−0.09	−0.99, 0.22	0.21	−0.1	−1.08, 0.25	0.22
	5th WA%	0.34	2.53, 6.3	<0.01	0.29	1.68, 6.15	< **0.01**
B^{10}	3rd Al/BSA	−0.07	−2.22, 0.72	0.31	−0.05	−2.15, 1.04	0.49
	3rd WA%	0.04	−1.73, 3.07	0.58	−0.02	−3.15, 2.49	0.82
	4th Al/BSA	−0.09	−2.01, 0.48	0.22	−0.09	−2.1, 0.61	0.28
	4th WA%	0.3	2.18, 6.24	<0.01	0.25	1.19, 5.98	< **0.01**
	5th Al/BSA	−0.22	−2.45, −0.44	<0.01	−0.24	−2.72, −0.54	< **0.01**
	5th WA%	0.44	3.86, 7.46	<0.01	0.4	3.31, 7.53	< **0.01**

**P* values were tested for correlation between CRS and airway dimension of each bronchi by the univariate linear regression analysis.
†P values were tested for correlation between CRS and airway dimension of each bronchi by the multivariate linear regression analysis adjusted for age, smoking-status, chest symptom, and asthma.
Al, airway luminal area; BSA, body surface area; WA, airway wall area, 95% CI, 95% confidence interval.

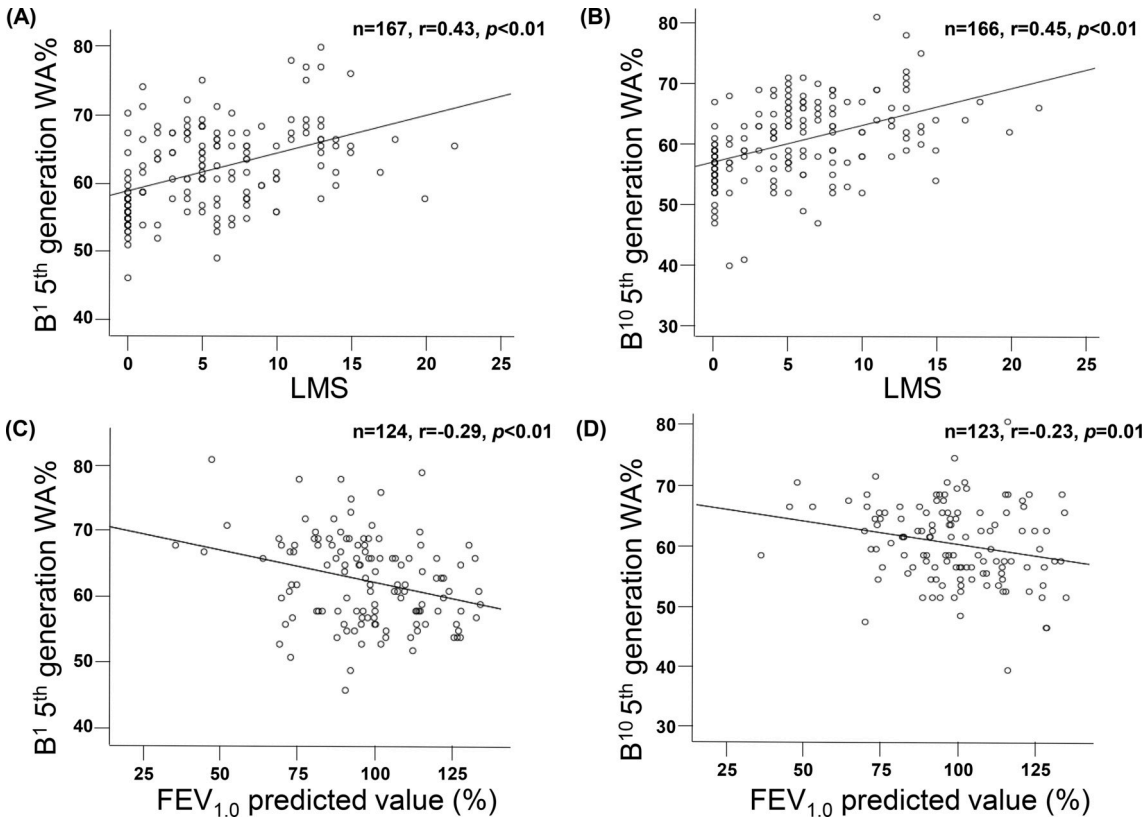

Fig. 2. Relationship between airway dimensions and clinical parameters in all subjects.
Pearson's correlation coefficient showed a significant positive correlation between airway wall area and Lund-Mackay score at (A) $B^1 5^{th}$ generation and (B) $B^{10} 5^{th}$ generation bronchi, and a negative correlation between airway wall area and % of forced expiratory volume in the 1-second predicted value at (C) B15th generation and (D) $B^{10} 5^{th}$ generation bronchi. WA, airway wall area; LMS, Lund-Mackay score, $FEV_{1.0}$, forced expiratory volume in 1 second.

Table 5
Relationship airway dimensions and clinical parameters in all subjects.

		Age (year)	Smoking (pack* year)	LMS	%$FEV_{1.0}$ (%)	$FEV_{1.0}$/FVC (%)	Neutrophils (/μL)	Eosinophils (/μL)	CRP (mg/dl)
n		172	150	172	127	127	162	129	129
B^1 WA%	3rd	−0.07	0.07	0.12	**−0.29****	−0.16	−0.01	0.12	0.04
	4th	−0.05	0.11	**0.38****	**−0.24****	**-.021***	−0.03	0.19*	0.004
	5th	−0.02	0.01	**0.44****	**−0.29****	**−0.28****	−0.04	0.18*	−0.01
B^{10} WA%	3rd	0.15	0.04	0.16	**−0.37****	**−0.29****	−0.05	**0.26****	0.04
	4th	0.1	0.08	**0.37****	**−0.27****	**−0.29****	−0.01	**0.28****	0.04
	5th	0.04	0.16	**0.45****	**−0.23****	**−0.24****	0.01	**0.36****	−0.01

P values were tested by Pearson's correlation coefficient.
*P < 0.05, **P < 0.01.
WA, airway wall area; LMS, Lund-Mackay score; $FEV_{1.0}$, forced expiratory volume in 1 s.

structural changes in the lower airways. In addition, several reports regarding the coexistence of CRS and COPD [4,6], bronchiectasis [7,8,38], or cystic fibrosis [38,39] suggest that the impact of CRS on lower airway diseases is beyond type 2 inflammation.

Our study has several limitations. First, this is a single-center, retrospective study. However, this may be a strong point. We consecutively analyzed all patients who have undergone CT in our hospital. As shown in Table 1, the reasons for taking sinus CT and chest CT were well distributed. Although most previous reports regarding CRS and lower airway diseases/pulmonary functions were analyzed using diagnosed patients of either upper or lower airway diseases, our study included subjects who were asymptomatic or did not have diagnosed airway diseases. It may help to understand the relationship between CRS and lower airway morphological changes in a more general population. Indeed, we found positive relationship between airway wall thickening and LMS even in the subjects who didn't have chest symptoms/diagnosed lung diseases at the point of taking chest CT. Secondly, not all subjects were evaluated by otolaryngologists or pulmonologists. Thus, overdiagnosis or underdiagnosis of CRS and lower airway diseases could have occurred. However, as shown in Table S4, the analysis of CRS patients diagnosed by otolaryngologists also showed the same tendency. Thirdly, we did not evaluate upper and lower airways from a pathophysiological viewpoint. Thus, to understand the mechanism underlying CRS and airway wall thickening, further studies are needed.

In summary, quantitative analysis of sinus and chest CT indicated that CRS patients have thicker airway walls than non-CRS patients. In addition, bronchial wall thickening is related to the severity of CRS as evaluated by LMS. Our observation suggests a strong relationship between upper and lower airways as well as the usefulness of morphological study by 3D-CT for evaluating airway diseases.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Suguru Majima: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Keiko Wakahara:** Conceptualization, Methodology, Investigation, Formal analysis, Funding acquisition, Writing - original draft, Writing - review & editing. **Tomoko Nishio:** Investigation, Writing - original draft. **Naoki Nishio:** Methodology, Investigation, Writing - original draft. **Masaaki Teranishi:** Methodology, Investigation, Writing - original draft. **Shingo Iwano:** Methodology, Investigation, Writing - original draft. **Akihiro Hirakawa:** Formal analysis, Writing - original draft. **Naozumi Hashimoto:** Investigation, Writing - original draft. **Michihiko Sone:** Supervision, Writing - original draft. **Yoshinori Hasegawa:** Supervision, Writing - original draft.

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Appendix A. Supplementary data

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References

[1] G.J. Braunstahl, United airways concept: what does it teach us about systemic inflammation in airways disease? Proc. Am. Thorac. Soc. 6 (8) (2009) 652–654.
[2] G. Ciprandi, D. Caimmi, M. Miraglia Del Giudice, M. La Rosa, C. Salpietro, G. L. Marseglia, Recent developments in United airways disease, Allergy Asthma Immunol Res 4 (4) (2012) 171–177.
[3] A.C.A. Yii, T.R. Tay, X.N. Choo, M.S.Y. Koh, A.K.H. Tee, D.Y. Wang, Precision medicine in united airways disease: a "treatable traits" approach, Allergy 73 (10) (2018) 1964–1978.
[4] A.G. Hansen, L.J. Stovner, K. Hagen, A.S. Helvik, W.M. Thorstensen, S. Nordgard, et al., Paranasal sinus opacification in headache sufferers: a population-based imaging study (the HUNT study-MRI), Cephalalgia 37 (6) (2017) 509–516.
[5] D. Jarvis, R. Newson, J. Lotvall, D. Hastan, P. Tomassen, T. Keil, et al., Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe, Allergy 67 (1) (2012) 91–98.
[6] K. Hakansson, L. Konge, S.F. Thomsen, V. Backer, C. von Buchwald, Sinonasal inflammation in COPD: a systematic review, Eur. Respir. J. 42 (5) (2013) 1402–1411.
[7] E. Handley, C.H. Nicolson, M. Hew, A.L. Lee, Prevalence and clinical implications of chronic rhinosinusitis in people with bronchiectasis: a systematic review, J Allergy Clin Immunol Pract 7 (6) (2019) 2004–2012 e1.
[8] W.J. Guan, Y.H. Gao, H.M. Li, J.J. Yuan, R.C. Chen, N.S. Zhong, Impacts of co-existing chronic rhinosinusitis on disease severity and risks of exacerbations in Chinese adults with bronchiectasis, PloS One 10 (9) (2015), e0137348.
[9] D.E. Shaw, A.R. Sousa, S.J. Fowler, L.J. Fleming, G. Roberts, J. Corfield, et al., Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort, Eur. Respir. J. 46 (5) (2015) 1308–1321.
[10] A. ten Brinke, D.C. Grootendorst, J.T. Schmidt, F.T. De Bruine, M.A. van Buchem, P.J. Sterk, et al., Chronic sinusitis in severe asthma is related to sputum eosinophilia, J. Allergy Clin. Immunol. 109 (4) (2002) 621–626.
[11] T. Nishio, K. Wakahara, Y. Suzuki, N. Nishio, S. Majima, S. Nakamura, et al., Mixed cell type in airway inflammation is the dominant phenotype in asthma patients with severe chronic rhinosinusitis, Allergol. Int. 68 (4) (2019) 515–520.
[12] S. Tanaka, T. Hirota, A. Kamijo, H. Ishii, K. Hatsushika, S. Fujieda, et al., Lung functions of Japanese patients with chronic rhinosinusitis who underwent endoscopic sinus surgery, Allergol. Int. 63 (1) (2014) 27–35.
[13] S.Y. Lee, S.H. Yoon, W.J. Song, S.H. Lee, H.R. Kang, S.S. Kim, et al., Influence of chronic sinusitis and nasal polyp on the lower airway of subjects without lower airway diseases, Allergy Asthma Immunol Res 6 (4) (2014) 310–315.
[14] A. Niimi, H. Matsumoto, R. Amitani, Y. Nakano, M. Mishima, M. Minakuchi, et al., Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices, Am. J. Respir. Crit. Care Med. 162 (4 Pt 1) (2000) 1518–1523.
[15] M. Hoshino, S. Matsuoka, H. Handa, T. Miyazawa, K. Yagihashi, Correlation between airflow limitation and airway dimensions assessed by multidetector CT in asthma, Respir. Med. 104 (6) (2010) 794–800.
[16] M. Hasegawa, Y. Nasuhara, Y. Onodera, H. Makita, K. Nagai, S. Fuke, et al., Airflow limitation and airway dimensions in chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 173 (12) (2006) 1309–1315.
[17] T. Achenbach, O. Weinheimer, A. Biedermann, S. Schmitt, D. Freudenstein, E. Goutham, et al., MDCT assessment of airway wall thickness in COPD patients using a new method: correlations with pulmonary function tests, Eur. Radiol. 18 (12) (2008) 2731–2738.
[18] F. Capraz, E. Kunter, H. Cermik, A. Ilvan, S. Pocan, The effect of inhaled budesonide and formoterol on bronchial remodeling and HRCT features in young asthmatics, Lung 185 (2) (2007) 89–96.
[19] S. Ishii, M. Iikura, M. Hojo, H. Sugiyama, Use of 3D-CT airway analysis software to assess a patient with severe persistent bronchial asthma treated with bronchial thermoplasty, Allergol. Int. 66 (3) (2017) 501–503.
[20] M. Zanon, D.L. Strieder, A.S. Rubin, G. Watte, E. Marchiori, P.F.G. Cardoso, et al., Use of MDCT to assess the results of bronchial thermoplasty, Am. J. Roentgenol. 209 (4) (2017) 752–756.
[21] W.J. Fokkens, V.J. Lund, J. Mullol, C. Bachert, I. Alobid, F. Baroody, et al., European position paper on rhinosinusitis and nasal polyps 2012, Rhinol Suppl. 23 (2012) 3.
[22] S.E. Kountakis, P. Arango, D. Bradley, Z.K. Wade, L. Borish, Molecular and cellular staging for the severity of chronic rhinosinusitis, Laryngoscope 114 (11) (2004) 1895–1905.
[23] N. Ashraf, N. Bhattacharyya, Determination of the "incidental" Lund score for the staging of chronic rhinosinusitis, Otolaryngol. Head Neck Surg. 125 (5) (2001) 483–486.
[24] P.A. de Jong, N.L. Muller, P.D. Pare, H.O. Coxson, Computed tomographic imaging of the airways: relationship to structure and function, Eur. Respir. J. 26 (1) (2005) 140–152.
[25] M. Hackx, A.A. Bankier, P.A. Gevenois, Chronic obstructive pulmonary disease: CT quantification of airways disease, Radiology 265 (1) (2012) 34–48.
[26] C. Hopkins, J.P. Browne, R. Slack, V. Lund, P. Brown, The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict? Otolaryngol. Head Neck Surg. 137 (4) (2007) 555–561.
[27] C.H. Martinez, Y.H. Chen, P.M. Westgate, L.X. Liu, S. Murray, J.L. Curtis, et al., Relationship between quantitative CT metrics and health status and BODE in chronic obstructive pulmonary disease, Thorax 67 (5) (2012) 399–406.
[28] P.M. Jairam, Y. van der Graaf, J.W. Lammers, W.P. Mali, P.A. de Jong, P.S. group, Incidental findings on chest CT imaging are associated with increased COPD exacerbations and mortality, Thorax 70 (8) (2015) 725–731.
[29] K. Nishimoto, M. Karayama, N. Inui, K. Mori, M. Kono, H. Hozumi, et al., Relationship between fraction of exhaled nitric oxide and airway morphology assessed by three-dimensional CT analysis in asthma, Sci. Rep. 7 (1) (2017) 10187.
[30] F.A. Mohamed Hoesein, P.A. de Jong, J.W. Lammers, W.P. Mali, M. Schmidt, H. J. de Koning, et al., Airway wall thickness associated with forced expiratory volume in 1 second decline and development of airflow limitation, Eur. Respir. J. 45 (3) (2015) 644–651.
[31] E.C. Oelsner, B.M. Smith, E.A. Hoffman, R. Kalhan, K.M. Donohue, J.D. Kaufman, et al., Prognostic significance of large airway dimensions on computed tomography in the general population. The Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study, Ann Am Thorac Soc 15 (6) (2018) 718–727.
[32] J.P. Charbonnier, E. Pompe, C. Moore, S. Humphries, B. van Ginneken, B. Make, et al., Airway wall thickening on CT: relation to smoking status and severity of COPD, Respir. Med. 146 (2019) 36–41.
[33] H. Kimura, S. Konno, Y. Nakamaru, H. Makita, N. Taniguchi, K. Shimizu, et al., Sinus computed tomographic findings in adult smokers and nonsmokers with asthma. Analysis of clinical indices and biomarkers, Ann Am Thorac Soc 14 (3) (2017) 332–341.
[34] T. Tokunaga, M. Sakashita, T. Haruna, D. Asaka, S. Takeno, H. Ikeda, et al., Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study, Allergy 70 (8) (2015) 995–1003.
[35] A. Kato, Immunopathology of chronic rhinosinusitis, Allergol. Int. 64 (2) (2015) 121–130.
[36] M. Okano, S. Kariya, N. Ohta, Y. Imoto, S. Fujieda, K. Nishizaki, Association and management of eosinophilic inflammation in upper and lower airways, Allergol. Int. 64 (2) (2015) 131–138.
[37] J.V. Fahy, Type 2 inflammation in asthma–present in most, absent in many, Nat. Rev. Immunol. 15 (1) (2015) 57–65.
[38] M.R. Loebinger, D. Bilton, R. Wilson, Upper airway 2: bronchiectasis, cystic fibrosis and sinusitis, Thorax 64 (12) (2009) 1096–1101.
[39] D.L. Hamilos, Chronic Rhinosinusitis in patients with cystic fibrosis, J Allergy Clin Immunol Pract 4 (4) (2016) 605–612.