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Evaluation of airway wall thickness via high resolution computerized tomography (HRCT) in mild intermittent asthma

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The study was performed at Van Higher Education Training and Research Hospital, Van, Turkey.

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions were as follows: SA: Literature search, Data collection, Study design, Manuscript preparation; MA: Analysis of data; BO: Review of manuscript.

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Abstract

Introduction: This study aims to evaluate bronchial thickness via thorax HRCT in subjects with mild intermittent asthma in comparison to healthy control subjects.

Methods: A total of 37 outpatients (mean (standard deviation; SD) age: 36.7 (9.7) years, 54.8% males) with mild intermittent asthma and 13 healthy controls (mean (SD) age: 25.0 (2.9) years, 61.5% males) were included in this case control study. Data on demographics, respiratory function tests segmental and subsegmental thorax HRCTs were recorded. The ratio of the bronchial wall thickness to the bronchial lumen diameter (T/D) and bronchial wall area percentage (WA %) were calculated for all cases.

Results: Subject and control groups were similar in terms of respiratory function tests, total and subsegmental T/D. Subsegmental WA% values at the level of inferior pulmonary vein (55.6(16.8) vs. 41.7(7.4); p=0.047) and 2 cm above the diaphragm (49.8(15.8) vs. 38.6(10.4); p=0.046) were significantly higher in subjects than controls. No significant correlation of overall and subsegmental T/D and WA% values to age in both groups and to asthma duration in subjects.

Conclusion: Our findings revealed increase in bronchial wall thickness in peripheral airways in subjects with mild intermittent asthma regardless of the duration of asthma. This may indicate the need to administration of anti-inflammatory or bronchodilator therapy effective on peripheral airways also in the early period.

Keywords: *Asthma; mild intermittent asthma; thorax high resolution computed tomography; respiratory function tests; bronchial wall thickening*

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Introduction

Asthma results in irreversible airflow obstruction in a subgroup of individuals via mechanisms proposed to include remodeling in the airway but yet unclear[1] which leads considerable morbidity and account for a high percentage of the health costs of asthma in these subjects.[2]

Characterized by an increase in the thickness of the airway wall, which results from mucosal infiltration by inflammatory cells, deposition of connective tissue on the extracellular matrix, and an increase in muscle mass, mucus glands and vessel area,[3] remodeling of the airway wall in subjects with asthma has been demonstrated to occur not only in the central, but also in the peripheral small airways.[4] The remodeling of small airways, in particular, may be largely responsible for irreversible airflow obstruction and an increase in airway responsiveness.[5] It is therefore important to assess the structural changes in the airway when deciding on the most appropriate asthma therapy for individual asthmatics.[5]

Remodeling is routinely evaluated based on certain parameters including internal and external diameters, the area of bronchial cross-section or bronchial lumen and their derivative indexes.[6] The use of dynamics of these parameters in making diagnostic decisions has been considered to necessitate use of measurement techniques enabling precise and reproducible assessment of the bronchial tree components.[6] Recently, owing to improved resolution enabling identification of features of 100–200 μm size and allowing assessment of small airways in the region of 1.5–2 mm diameter,[7] high resolution computed tomography (HRCT) has gained increasing interest in this context. HCRT has been advocated for assessing the structural changes in the asthmatic lung in relation to severity of the disease and clinical parameters.[2,5]

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The present study was designed to evaluate bronchial thickness via thorax HRCT in subjects with mild intermittent asthma receiving as needed short acting β2 agonists but not inhaler corticosteroids (ICS) in comparison to healthy control subjects. Additionally the relation of bronchial thickness to age, respiratory function tests and asthma duration was evaluated.

Methods

Study population

A total of 50 participants including 37 outpatients (mean (standard deviation; SD) age: 36.7(9.7) years, 54.8% males) with mild intermittent asthma and 13 healthy controls (mean (SD) age: 25.0 (2.9) years, 61.5% males) were included consecutively in this case control study. All patients were previously diagnosed based on spirometry and methacholine challenge tests with asthma at the chest diseases outpatient clinic with no exacerbation within the past 6 months, therefore currently classified as having mild intermittent asthma. Therefore, repeat of methacholine inhalation test was not considered necessary.

Female or male outpatients ≥18 years of age, diagnosed with mild intermittent asthma (daytime symptoms for less than twice per week, nocturnal symptoms for less than twice per month, feeling completely normal during the symptom-free periods and daily PEF variability for less than 20%), no exacerbations within the last 6 months, receiving no asthma related treatment other than the short acting β_2 agonist inhaler therapy, non-smoker, without past history of a regular treatment for another disease (inactive lung tuberculosis, bronchiectasis, lung malignancy, heart failure and diabetes mellitus), no history of upper respiratory airway infection within the last 6 weeks were included in the present study. Control group was composed of healthy non-smoker subjects without a past history of respiratory or allergic disease, upper respiratory airway infection within the last 6 weeks and regular treatment for another disease. Patients not meeting the inclusion

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criteria, patients with a known exposure to environmental pollutants such as motor exhaust, smoke, pesticides, solvents and molds from wet agricultural environments, patients with obstructive sleep apnea based on presence of nighttime snoring and witnessed apnea along with identification of scores of >10 on Epworth Sleepiness Scale and patients who were confirmed to have additional cardiac pathologies were excluded from the study.

Asthma control level was classified as controlled, partly controlled and uncontrolled based on daytime symptoms, limitations of activities, nocturnal symptoms/awakening, need for reliever/rescue treatment, lung function and the number of exacerbations, while asthma attack severity was categorized into four groups as mild, moderate, severe and life-threatening based on Global Initiative for Asthma (GINA, 2007) guidelines.[8] In relation to replacement of the concept of disease severity with disease control in updated asthma guidelines,[9] subject population in the present study was determined to be composed of subjects with controlled asthma with as needed use of short acting β_2 agonist inhaler therapy.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee.

Data collection

Demographic (age, gender) and clinical features (duration of asthma, smoking status and past history of medical treatment) of subjects were recorded. Respiratory function tests and thorax HRCTs were performed at the same day with discontinuation of agonist therapy 12 or 24 hours prior to measurements in all cases as well as thorax HRCT slices that involved the segmental and subsegmental airways of the lung. The ratio of the bronchial wall

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thickness to the bronchial lumen diameter (T/D) and bronchial wall area percentage (WA%) were calculated for all cases.

High resolution computerized tomography (HRCT) measurements

HRCT measurements were performed by the same experienced radiologist in all cases using a multi detector computerized tomography (MDCT) system called Sensation 4 (Siemens, Erlangen, Germany) at 120 kV peak and 90 mA with scan collimation of 1.0 mm and section thickness of 2.0 mm. After initial evaluation of sections, bronchial thickness and bronchial diameter were measured at 5 different levels of both segmental and subsegmental layers. Window width and level used in assessment of wall thickness were based on characteristics dictated by results of the validation studies conducted with phantom models and cadaveric lungs.[10,11] HRCT sections were taken from superior margin of aortic arch, 1 cm above the carina, carina, the level of inferior pulmonary vein and 2 cm above the diaphragm (Fig 1). Given the statement on the influence of oblique sections on bronchial wall thickness,[12] the ratio of long to short diameter of bronchus being assessed was paid attention to be less than 1.5. To overcome the probability of individual variability in measurements certain ratios were calculated including a) bronchial wall thickness; expressed as a ratio to the total airway diameter (T/D) and calculated using formula of bronchial wall thickness/bronchial lumen diameter and b) bronchial wall area; expressed as a percentage of total airway cross sectional area (WA%) using the formula of bronchial area-luminal area/bronchial area (Fig 2).

Spirometric measurements

Spirometric measurements were made via Vitalograph Alpha (serial No. /serien No AL 12907) device to evaluate FEV1 (forced expiratory volüme in one second), FEV1/FVC and PEF (peak expiratory flow) parameters.

Statistical analysis

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Statistical analysis was made using computer software (SPSS version 13.0, SPSS Inc. Chicago, IL, USA). Student T test was used for comparison of T/D and WA(%) values between subject and control groups. The relation of RFT to demographics and asthma duration was evaluated using Pearson correlation analysis. Data were expressed as "mean (SD)" and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

Results

Asthma subjects were significantly older (36.7(9.7) vs. 25.0(2.9) years, $p<0.001$) compared with control group, but there was no significant difference regarding gender distribution (males 54.8 vs. 61.5%, $p<0.640$). Mean(SD) asthma duration was 42.7 (6.0) months in subjects with mild intermittent asthma (Table 1).

There was no gender influence on total mean(SD) T/D (0.32(0.08) in males vs. 0.30(0.07) in females) and total mean(SD) WA% (47.4(9.6) in males vs. 48.4(8.7) in females) values.

Bronchial wall thickness ratio (T/D) in subject vs. control groups

Subject and control groups were similar in terms of total thickness as well as thickness measured from sections taken from superior margin of aortic arch, 1 cm above the carina, carina, at the level of inferior pulmonary vein and 2 cm above the diaphragm (Table 1).

Bronchial wall area percentage (WA%) in subject vs. control groups

Besides overall mean(SD) WA% (50.9(10.0) vs. 42.0(7.0); $p<0.004$) values, subsegmental WA% values for the level of inferior pulmonary vein (55.6(16.8) vs. 41.7(7.4); $p=0.047$) and 2 cm above the diaphragm (49.8(15.8) vs. 38.6(10.4); $p=0.046$) were also significantly higher in the subject group compared with control subjects (Table 1).

Respiratory function tests in subject vs. control groups

Subject and control groups were similar in terms of mean (SD) FEV1, FEV1/FVC and PEF values (Table 1).

Correlation of T/D and WA% to age, respiratory function tests and asthma duration

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In both asthmatic and control subjects, there was no significant correlation of overall and subsegmental T/D and WA% values to age, asthma duration and respiratory function tests.

Discussion

Our findings related to evaluation of bronchial wall thickness ratio (T/D) and bronchial wall area percentage (WA%) in subjects with mild intermittent asthma in comparison to healthy controls revealed no difference between subjects and controls in terms of segmental and subsegmental T/D, whereas significantly higher total segmental and subsegmental WA% including level of inferior pulmonary vein and 2 cm above the diaphragm in the subjects than controls. In both groups; age, asthma duration and respiratory function test results were not correlated to T/D and WA%.

In recent years, HRCT become available in the clinical practice as a non-invasive method enabling objective evaluation of lung parenchyma and bronchial wall thickening in parallel to asthma severity[2,13,14] with no inter-observer difference indicating the reproducibility of the method.[2]

Supporting the concept of chronic inflammation causing bronchial wall thickening and remodeling, the main findings in the literature suggest that subjects with asthma have greater airway wall thickening than normal subjects and that those with severe disease have thicker airways than subjects with milder disease.[15]

In the present study airway dimensions of both segmental and subsegmental bronchi were measured directly from magnified HRCT images and results were expressed based on calculation of the ratio of airway wall thickness to outer diameter (T/D) and the percentage wall area (WA%). While similar studies in the literature evaluated bronchial wall thickness based on measurement of T/D ratio only by Boulet et al.[16] and calculation of WA% per se by Okazawa et al,[17] we used both T/D and WA% to assess thickening of the segmental and subsegmental bronchi alike to studies conducted by Awadh et al.,[13] Niimi et al.,[18] and

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Gono et al.[5] Results of these studies revealed inconsistent data including no bronchial wall thickening in large airways,[16] increased thickness in large airways,[18] in airways smaller than 6 mm in luminal diameter,[17] and also in both large and small airways[13] among asthmatics compared to controls; as well as in asthmatics with deficient reversible airflow obstruction compared to asthmatics with normal spirometric functions.[5]

However given the higher degree of airway thickening in subjects with nearly fatal and moderate asthma than subjects with mild asthma,[13] inclusion of controlled subjects with mild intermittent asthma in the present study seems consistent with our findings of similar T/D values for both segmental and subsegmental airways between subject and control groups.

Accordingly, significantly higher subsegmental WA% values for the measurements at the level of inferior pulmonary vein and 2 cm above the diaphragm in the subject than control group in the present study seem to indicate that increased bronchial wall thickness among mild intermittent asthma subjects was specific to small peripheral airways as also confirmed in a past study on childhood asthma.[19]

Besides, increased segmental and subsegmental bronchial wall area in our subjects compared to controls supports that the use of WA% in evaluation of both segmental and subsegmental bronchial walls was associated with increased bronchial wall thickness in both small and large airways in mild to moderate[13,17] and nearly fatal asthma subjects with thickening directly proportional to severity of the disease.[13] Likewise, given the inflammation involves the whole wall of the bronchus leading an obstruction, measurements taken from a single point was reported to be associated with incorrect findings, while WA% was indicated to be more relevant method in reflection of the changes in bronchial wall thickness.[20]

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The pathological features of bronchial wall thickening may reflect not only irreversible airway remodeling such as hypertrophy of mucus-secreting glands, subepithelial fibrosis, marked thickening of basement membrane, hyperplasia and hypertrophy of airway smooth muscle, but also reversible components such as edema, infiltration by inflammatory cells and bronchoconstriction.[5] Hence, asthma has been recommended to be optimally controlled before HRCT assessment to exclude the influence of the potentially reversible airway changes in a radiological study of airway structural changes.[2,21] In our study population composed of mild intermittent asthma subjects under disease control, HCRT measurements of both segmental and sub-segmental airways performed by the same experienced radiologist. Our findings revealed that subjects and controls were similar in terms of total and subsegmental bronchial wall thickness, while significantly higher bronchial wall area was determined in terms of total segmental and sub-segmental regions consistent with the predominant involvement of peripheral small airways in subjects than control subjects.

Likewise, Gono et al.[5] evaluated the irreversible structural changes of airways with the aid of HRCT scanning via inclusion of stable and asymptomatic asthmatics as well as elimination of the reversible components. They concluded that asthmatics with incomplete reversibility of airflow obstruction showed an increased airway wall thickness on HRCT compared with asthmatics with complete reversibility of airflow obstruction alike to other studies.[22,23]

Accordingly lack of significant difference between our subjects with mild intermittent controlled asthma and normal controls in terms of T/D and respiratory function parameters is consistent with the significant correlation between the wall thickness and airflow obstruction and the similarity of asymptomatic asthmatics without airflow obstruction to normal subjects as reported by Gono et al.[5]

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Data on the correlations of wall thickness and area to lung function are inconsistent and potentially compromised due to lack of elimination of reversible changes of airways.[18] Hence, lack of any correlation between respiratory function parameters and segmental T/D and WA% values in the present study is in line with the past studies indicating that airway wall thickening was not correlated with airflow obstruction.[16,22,24,25] However this finding is unlike to the statement that thickening induces airflow obstruction in subjects with asthma based on reported significant and negative correlation between indices of airway wall thickness and FEV1%.[12]

Carina was the only subsegmental region in our study where the bronchial thickness showed a significant correlation with FEV1/FVC in terms of T/D in subjects and both of T/D and WA% in controls. However, there was no marked increase in either bronchial wall thickness or area in this subsegmental area compared to controls. Hence, our findings seem to support that thickening of the airway wall assessed by HRCT scanning seems not correlated with airflow obstruction and that small airway function may be influenced more by bronchial wall thickening than is respiratory function parameters.[2,22]

In fact, in a past study concerning bronchoarterial ratio and bronchial wall thickness on high-resolution CT in asymptomatic subjects, the bronchoarterial ratio was reported to be influenced by aging with HRCT analyzed bronchioarterial ratio significantly higher in patients over 65 years of age. Hence, it was stated that when this ratio is used for the quantitative analysis of pulmonary and cardiovascular disease, the influence of age should be considered.[26]

However, albeit subject and control groups in the present study were not homogenous in terms of age and gender distribution, there was no significant relation of bronchial wall thickness measurements to age and gender both in subject and control groups. Hence our findings seem to be free of possible compromising influence of age and gender disparity.

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Nevertheless, it is obvious that these findings should be justified by future larger scale studies to be confident of this statement. Besides asthma duration had no significant influence on bronchial wall thickness and area alike to lack of association of asthma duration with bronchial thickness, as reported in subjects with mild persistent and persistent asthma by Chetta et al.[27]

Given the significant alterations in bronchial wall thickness associated with smoking[26], exposure to environmental pollutants[28] and presence of OSA[29], it is worth noting that our study population of mild asthmatics was composed of non-smoker individuals without OSA and history of exposure to environmental pollutants.

Identification of bronchial wall thickening and increased cross sectional area particular to peripheral airways in the present study seems to support that even subjects with mild asthma had thickening of the airway wall compare with normal controls.[13] Besides, given that subjects with mild asthma had a long history of asthma despite no admission to hospital and normal baseline lung function tests, it was hypothesized that chronic inflammatory changes lead to airway wall thickening even in subjects with mild disease. Hence, albeit inhaled corticosteroids could not be administered in our subjects since they were not meeting the criteria of taking inhaled corticosteroids according to guidelines, as shown in previous studies[30-32] the possibility of prevention of the development of chronic airway obstruction with the early use of inhaled corticosteroids seems notable and has been emphasized in some national guidelines.[13,32]

However, it must be emphasized that the difference between subjects with mild asthma and normal subjects in terms of airway wall thickening was reported to be small with unknown clinical significance.[13] A considerable overlap between asthmatic and normal subjects was indicated to support the view that this aspect of airway remodeling does not necessarily discriminate individual asthmatic subjects from normal subjects, whereas generally present

in asthmatic subjects as a group which may be related to physiological change and can be positively affected by long term ICS.[25,33]

Major limitation of our study is the small sample size which limits generalizability of our findings by making them arguable in terms of statistical power, whereas inclusion criteria are in accordance with the good control of external effects and international guidelines are well-followed. Hence, our study has merit and is relevant from a clinical point of view as it suggests that even mild intermittent asthma may induce structural changes in the small airways.

In conclusion, our findings revealed significant increases in bronchial wall thickness considering peripheral airways in subjects with mild intermittent asthma regardless of the duration of asthma. To be justified via future randomized controlled trials, this may indicate the need to administration of anti-inflammatory or bronchodilator therapy effective on peripheral airways also in the early period. Besides, our findings confirm that HCRT is a suitable noninvasive method in measurement of bronchial wall thickness.

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LEGEND TO THE FIGURES

Fig 1. Subsegmental HRCT sections for bronchial wall thickness

A. superior margin of aortic arch, B. 1 cm above the carina, C. carina, D. the level of inferior pulmonary vein, and E. 2 cm above the diaphragm. Sections were determined by an experienced radiologist and measurements were made via electronic caliper at 5X magnification.

Fig 2. Calculation of bronchial wall thickness ratio (T/D) and bronchial wall area percentage (WA%)

T/D: bronchial wall thickness ratio; WA%: bronchial wall area percentage; T: bronchial wall thickness; D: bronchial lumen diameter; Ao: bronchial area; A1: luminal area.

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Table 1. Comparison of subject and control groups in terms of study parameters

	Asthmatics (n=37)	**Controls (n=13)**	**p value**
	n(%)		
Male gender	20(54.8)	8(61.5)	**0.640**
	Mean (SD)		
Age (years)	36.7(9.7)	25.0(2.9)	**<0.001**
Duration of asthma (months)	42.7(6.0)	-	-
Bronchial wall thickness ratio (T/D)			
T/D at the superior margin of aortic arch	0.30(0.11)	0.35(0.06)	0.060
T/D at 1 cm above the carina	0.29(0.12)	0.35(0.07)	0.067
T/D at the carina	0.30(0.15)	0.36(0.06)	0.151
T/D at the level of inferior pulmonary vein	0.29(0.15)	0.33(0.07)	0.212
T/D at 2 cm above the diaphragm	0.31(0.14)	0.38(0.11)	0.060
Total thickness	0.30(0.09)	0.36(0.06)	0.470
Bronchial wall area percentage (WA%)			
WA% at the superior margin of aortic arch	48.0(17.1)	41.9(6.6)	0.147
WA% at 1 cm above the carina	47.5(12.9)	40.5(9.1)	0.050
WA% at the carina	53.7(16.7)	47.3(16.7)	0.083
WA% at the level of inferior pulmonary vein	55.6(16.8)	41.7(7.4)	**0.047**
WA% at 2 cm above the diaphragm	49.8(15.8)	38.6(10.4)	**0.046**
Total area	50.9(10.0)	42.0(7.0)	**0.004**
Respiratory function tests			
FEV1	86.0(7.8)	93.1(10.9)	0.120
FEV1/FVC	84.5(6.1)	88.8(4.8)	0.254
PEF	85.5(1.5)	90.4(5.4)	0.110

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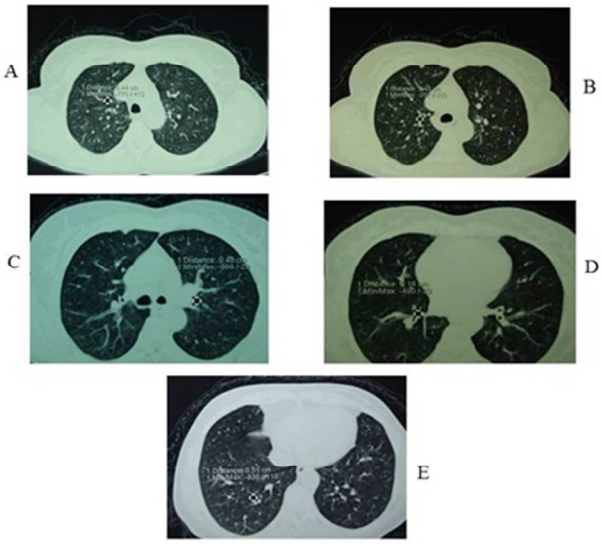

Fig 1. Subsegmental HRCT sections for bronchial wall thickness
A. superior margin of aortic arch, B. 1 cm above the carina, C. carina, D. the level of inferior pulmonary vein, and E. 2 cm above the diaphragm. Sections were determined by an experienced radiolog and measurements were made via electronic caliper at 5X magnification.

192x115mm (96 x 96 DPI)

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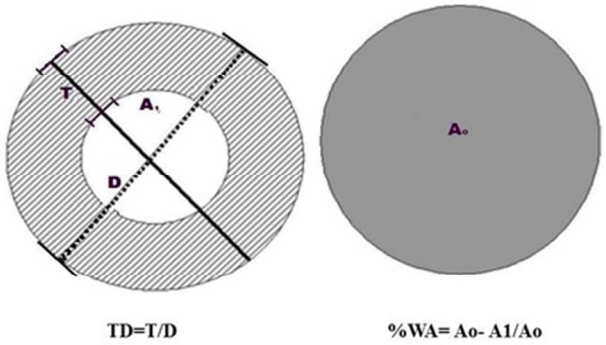

Calculation of bronchial wall thickness ratio (T/D) and bronchial wall area percentage (WA%)
T/D: bronchial wall thickness ratio; WA%: bronchial wall area percentage; T: bronchial wall thickness; D: bronchial lumen diameter; Ao: bronchial area; A1: luminal area.

192x115mm (96 x 96 DPI)