ORIGINAL ARTICLE

Endothelial Dysfunction and Pentraxin-3 in Clinically Stable Adult Asthma Patients

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Abstract

Background: Asthma is associated with low-grade systemic inflammation, prothrombotic state, and premature atherosclerosis.
Objective: To evaluate the relationships between asthma, inflammatory biomarkers, and parameters of endothelial dysfunction.
Material and Methods: We analyzed flow-mediated dilatation (FMD) of the brachial artery and intima-media thickness (IMT) of the common carotid artery using ultrasound in 92 clinically stable adult asthmatics and 62 well-matched controls. We also measured blood levels of selected inflammatory and asthma-specific biomarkers, including interleukin (IL) 4, IL-5, IL-6, IL-10, IL-12 (p70), IL-17A, IL-23, and interferon γ, as well as a disintegrin and metalloproteinase domain–containing protein 33 (ADAM-33). In addition, we assessed endothelial damage using 2 laboratory biomarkers: circulating von Willebrand factor (vWF) and pentraxin-3. We analyzed relationships between the study variables and asthma severity, lung function abnormalities, airway remodeling indices on computed tomography, and transthoracic echocardiography parameters.
Results: Asthmatics had higher IL-6, IL-10, and ADAM-33 levels. They were also characterized by 23% lower FMD% and 15% thicker IMT, as compared with controls (*P*<.001, both). In asthma, vWF was related to age (ß=0.28 [95%CI, 0.15-0.41]) and remained inversely associated with FEV_1 (ß=–0.2 [95%CI, –0.05 to –0.35]). Surprisingly, a negative correlation was revealed between vWF and pentraxin-3 (ß=–0.17 [95%CI, –0.3 to –0.04]). Pentraxin-3 remained positively associated with airway remodeling indices.
Conclusions: Asthma is characterized by endothelial dysfunction associated with airway obstruction. The biological role of pentraxin-3 is unknown, although our data suggest a protective role against endothelial damage and atherosclerosis.

Key words: Asthma. Endothelium. Flow-mediated dilatation. Intima-media thickness. Pentraxin-3.

Resumen

Antecedentes: El asma se asocia con inflamación sistémica de bajo grado, con un estado protrombótico y la existencia de aterosclerosis prematura.
Objetivo: Evaluar las relaciones entre asma, biomarcadores inflamatorios y parámetros de disfunción endotelial.
Material y métodos: Se ha analizado la dilatación mediada por flujo (DMF) de la arteria braquial y el grosor íntima-media (GIM) de la arteria carótida común mediante ecografía, en 92 adultos asmáticos clínicamente estables y 62 controles. También se midieron los niveles sanguíneos de determinados biomarcadores inflamatorios específicos de asma, incluyendo interleucina (IL) -4, IL-5, IL-6, IL-10, IL-12 (p70), IL-17A, IL-23, interferón γ, así como desintegrina y la metaloproteinasa que contiene el dominio proteína 33 (ADAM-33), junto con marcadores de laboratorio de daño endotelial: pentraxina-3 circulante y actividad plasmática del factor von Willebrand (vWF). Analizamos las relaciones de las variables estudiadas con la gravedad del asma, las anomalías de la función pulmonar, los índices de tomografía computarizada (TC) pulmonar de remodelación de las vías respiratorias y los parámetros de ecocardiografía transtorácica.
Resultados: Los asmáticos tuvieron mayores niveles de IL-6, IL-10 y ADAM-33. También se caracterizaron por tener un 23% menos de DMF y un 15% más grueso el GIM, en comparación con los controles (p <0,001, ambos). En el asma, vWF se relacionó con la edad (ß = 0,28 [IC 95%: 0,15 a 0,41]) y se mantuvo en una relación inversa con FEV_1 (ß = -0,2 [IC 95%: -0,05 a -0,35]). Sorprendentemente, se observó una correlación negativa entre vWF y pentraxina-3 (ß = -0,17 [IC 95%: -0,3 a -0,04]). La pentraxin-3 se asoció positivamente con los índices CT de remodelación de la vía aérea.
Conclusiones: El asma se caracteriza por una disfunción endotelial relacionada con la obstrucción de las vías respiratorias. Se desconoce el papel biológico de la pentraxina-3, aunque nuestros datos sugieren su papel protector contra el daño endotelial y la aterosclerosis.

Palabras clave: Asma. Endotelio. Dilatación mediada por flujo. Espesor íntima-media. Pentraxina-3.

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Introduction

Asthma is a chronic inflammatory disease of the airways [1]. A growing body of evidence supports its association with low-grade systemic inflammation, prothrombotic state [2,3], and premature development of atherosclerosis [4], accompanied by an increased risk of cardiovascular events, including cardiac death [5-8]. Atherosclerosis affects the arterial wall but is also related to inflammation [9]. Premature atherosclerosis has been demonstrated in patients with various inflammatory diseases, such as lupus erythematosus [10], systemic sclerosis [11,12], and vasculitis [13,14]. In addition to inflammation, other, well-established cardiovascular risk factors that might play a proatherogenic role in asthma include obesity, smoking, lack of physical activity, airway obstruction resulting in hypoxia, and corticosteroid therapy [6]. Few studies document premature development of atherosclerosis in asthmatics, including children [15-19]. However, the exact mechanisms and pathogenesis of these unfavorable blood vessel alterations remain unknown and require further investigation.

Endothelial cell dysfunction is a major cause of atherosclerotic cardiovascular diseases. It is related to the various nonadaptive alterations in arterial endothelial function, which may have important implications for the regulation of blood vessel hemostasis, local thrombosis, maintenance of vascular tone, and inflammatory response within the arterial wall [20]. Impaired endothelial function, together with atherosclerotic plaque rupture and subsequent thrombosis, is the main contributor to acute and chronic myocardial ischemia [21,22], although this impairment might be reversed by appropriate therapy or lifestyle changes. Endothelial function can be evaluated by measuring changes in arterial diameter in response to vasoactive agents, such as nitric oxide injected directly into the affected artery [23]. However, this approach is invasive and not routinely recommended. In turn, evaluation of flow-mediated dilatation (FMD) and calculation of the vascular reactive hyperemia index of the brachial artery are noninvasive and simple alternatives that can be used in clinical practice [24]. These approaches measure endothelium-dependent dilatation of the brachial artery in response to reactive hyperemia (shear stress) with subsequent endogenic nitric oxide release.

Pentraxin-3 is an acute phase glycoprotein that is similar in structure to C-reactive protein (CRP). It has been suggested that CRP is a marker of systemic inflammation, whereas pentraxin-3, which is synthesized locally by the endothelial cell, is involved in vascular system abnormalities [25,26]. Circulating pentraxin-3 is increased in patients with cardiovascular diseases [27], obstructive sleep apnea [28], and autoimmune conditions, including rheumatoid arthritis, systemic sclerosis, and vasculitis [25].

Using available data on potential links between asthma, inflammation, thrombosis, and atherosclerosis, we sought to evaluate endothelial function in clinically stable adults with asthma by measuring FMD and the intima-media thickness (IMT) of the common carotid artery as markers of atherosclerosis. We also analyzed selected inflammatory and asthma-specific parameters, as well as laboratory biomarkers of endothelial damage, including circulating von Willebrand factor (vWF) and pentraxin-3 [29,30]. We studied associations between the study variables, asthma severity score, lung function abnormalities, airway remodeling indices on computed tomography (CT), and transthoracic echocardiography parameters. To our knowledge, no such studies have previously been conducted.

Methods

We performed a retrospective study, which was approved by the Bioethics Committee of Jagiellonian University Medical College. Participation was voluntary, and all the individuals were informed about the methodology and potential adverse effects. Written informed consent was provided by both patients and controls.

Participants

We enrolled 92 White adults (66 women and 26 men) with clinically stable asthma from 2012 to 2016 at the Outpatient Clinic of the Department of Allergy and Clinical Immunology, University Hospital, Krakow, Poland. All patients were diagnosed with asthma based on the clinical history (wheezing, shortness of breath, dyspnea, and cough) and a postbronchodilator increase in forced expiratory volume in 1 second (FEV_1) of at least 12% and 200 mL, either currently or previously. All asthma medications, except for biological treatment, were permitted. Oral corticosteroids were allowed at a daily dose equivalent to ≤10 mg of prednisolone unless the doses had remained unchanged during the preceding 3 months. Asthma patients could not have experienced exacerbations during the preceding 6 months.

The control group consisted of 62 individuals (39 women and 23 men) matched with the asthma group by race, sex, age, body mass index (BMI), and internal medicine comorbidities, including arterial hypertension, hypercholesterolemia, and diabetes mellitus. Controls were enrolled from hospital personnel and their relatives and had no history of allergy or bronchial obstruction. Each control was individually matched with 2 patients, considering the closest values of the matching criteria.

The participants in both study groups were aged 18-70 years. The exclusion criteria for all participants were congestive heart failure, coronary heart disease, stroke, liver injury, chronic kidney disease (stage 3 or more), and ongoing cancer treatment. Definitions of all comorbidities have been provided in an online supplement.

Spirometry and Lung Computed Tomography

Spirometry and lung CT were performed only in patients with asthma.

Airway cross-sectional geometry was quantified automatically using AW Server Software (General Electric Healthcare) in 2 peripheral bronchi: the right and the left lower lobe basal posterior bronchi (RB10 and LB10, respectively). We previously demonstrated that both correlated best in CT metrics with spirometry variables and histological features of airway remodeling. Therefore, these metrics formed the basis of our current research [32]. In both peripheral airways, we assessed average lumen and airway diameter, average wall

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thickness, lumen and wall area, wall area ratio (WAR), and wall thickness ratio (WTR), as previously described [32]. Wall thickness was calculated based on average outer and inner bronchial diameters. The WAR was defined as an average difference between the outer wall area and the inner wall area divided by the outer wall area. The WTR was calculated as the average value of the ratio of the wall thickness and the airway diameter. CT-based indices were measured twice by an independent radiologist (JZ) on different days. The mean value was further analyzed. Further detail on CT and spirometry investigations is provided in the online supplement.

Ultrasound Examinations

Ultrasound studies were performed in a dark, quiet room with participants resting in a supine position for 10 minutes before the examination started. Examinations were conducted by 2 independent ultrasound experts using the Siemens Acuson Sequoia 512 with a 10-MHz linear array ultrasonic transducer (MountainView). Both experts made 3 consecutive measurements of each parameter (FMD and IMT). The result recorded was the mean of the 3 measurements for each parameter. Participants also underwent transthoracic echocardiography, with measurements of the left ventricular ejection fraction and systolic pulmonary artery pressure using standard procedures [33]. A detailed description of all ultrasound procedures is provided in the online supplement.

Laboratory Analysis

In the morning, fasting blood samples were drawn from the antecubital vein with minimal stasis into the serum tube and a tube containing 0.109 mol/L sodium citrate (vol/vol, 9:1). Samples were centrifuged at 2000*g* for 10 minutes at room temperature within 2 hours of collection. Routine laboratory techniques were used to perform basic laboratory tests. C-reactive protein was measured using the Johnson & Johnson VITROS 250 device.

Commercially available high-sensitivity enzyme-linked immunosorbent assays (ELISAs) were applied to analyze levels of IL-4, IL-5, IL-6, IL-10, IL-12(p70), IL-17A, IL-23, and INF-γ (eBiosciencea). A disintegrin and metalloproteinase domain-containing protein 33 (ADAM-33) was assessed in serum using standard ELISA (Cloud-Clone Corp). Pentraxin-3 was also analyzed (Elabscience). Blood concentrations of pentraxin-3 were measured calorimetrically according to the manufacturer's instructions, with a detection threshold of 0.252 ng/mL. The activity of vWF was analyzed in plasma using ELISA (Asserachrom, DiagnosticaStago).

Statistical Analysis

Results for the asthma and control groups were compared using Statistica 13.3 (TIBCO Software Inc). According to the Shapiro-Wilk test, continuous variables were all nonnormally distributed. Variables were compared using the Mann-Whitney test and are reported as median and interquartile range. Categorical variables were reported as percentages and compared using the χ^2 test. To adjust for potential confounders, the results of a relative increase in the FMD (FMD%), IMT, pentraxin-3, and vWF activity were Box-Cox normalized, and a 1-way analysis of covariance was performed adjusted for age, sex, and BMI. The univariate linear regression models adjusted for the same confounders were used to analyze associations between 2 selected parameters. Independent determinants of FMD% and IMT were established in multiple linear regression models built using a forward stepwise selection procedure verified by the Snedecor F-distribution. The R^2 was assessed as a measure of the variance. Unconditional multivariate logistic regression and a 1-way analysis of variance were used to analyze independent impact of comorbidities, including

Table 1. Demographic Factors, Comorbidities, and Asthma Severity Parameters in Asthmatics and Controls

	Patients n=92	Controls n=62	*P* Value
Age, y	54 (45-62)	48 (41.5-60)	.36
Male sex, No. (%)	26 (28.3)	23 (37.1)	.4
Body mass index, median (IQR), kg/m^2	27 (24.3-31.3)	26.8 (24.2-29.4)	.27
Other cardiovascular risk factors			
Hypertension, No. (%)	53 (47.3)	22 (39.3)	.08
Diabetes mellitus, No. (%)	18 (16.1)	5 (8.93)	.11
Hypercholesterolemia, No. (%)	28 (25)	18 (32)	.76
Smoking currently, No. (%)	8 (7.14)	3 (5.36)	.64
Smoking, median (IQR), pack-years	0 (0-18)	0 (0-3)	.1
Asthma severity (GINA)			
Mild, No. (%)	14 (15)	-	-
Moderate, No. (%)	37 (40)	-	-
Severe, No. (%)	41 (45)	-	-
Spirometry results			
FEV_1, median (IQR), % of predicted value	93 (68.1-108.1)	-	-
FEV_1/VC, median (IQR), %	68 (59.7-75.5)	-	-

Abbreviation: FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; VC, vital capacity.

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hypertension, diabetes mellitus, hypercholesterolemia, and statin therapy on FMD% and IMT, respectively. In order to calculate the odds ratio (OR) with a 95%CI, the cut-off point of FMD% was calculated based on receiver operating characteristic (ROC) curves. Statistical significance was set at $P<.05$.

Results

Patients and Controls

Table 1 shows the demographic and clinical characteristics of asthma patients and controls. Both groups were well matched according to the demographic variables, including age, sex, BMI, and smoking habit, as well as the prevalence of comorbidities managed in the internal medicine department, such as hypertension, diabetes mellitus, and hypercholesterolemia.

Basic Laboratory Tests, Inflammatory, and Asthma-Specific Biomarkers

The results of the basic laboratory tests are shown in Table 2 and in Table 1S of the online supplement. Asthmatics had higher serum triglycerides, as well as raised inflammatory markers, including white blood cell count, CRP, and circulating IL-6 and IL-10. They were also characterized by a 2-fold higher blood level of ADAM-33.

The plasma activity of vWF was similar in both groups (Table 2). In asthmatics, however, it remained inversely associated with FEV_1 (β=–0.2 [95%CI, –0.05 to –0.35]) and the FEV_1/FVC index (β=–0.24 [95%CI, –0.35 to –0.13]). Interestingly, in both groups, we documented positive relationships between plasma vWF activity and renal parameters (asthmatics, β=0.24 [95%CI, 0.06-0.42] and β=0.3 [95%CI, 0.15-0.45]; controls, β=0.24 [95%CI, 0.06-0.42] and

Table 2. Results of Selected Laboratory and Ultrasound Parameters in Both Studied Groups[a]

	Patients n=92	Controls n=62	*P* Value
Basic laboratory tests			
Total cholesterol, mmol/L	4.9 (4.2-5.7)	5 (4.2-5.3)	.88
Low-density lipoprotein cholesterol, mmol/L	2.67 (2.25-3.14)	3.2 (2.49-3.64)	<.001
High-density lipoprotein cholesterol, mmol/L	1.34 (1.09-1.6)	1.39 (1.18-1.8)	.27
Triglycerides, mmol/L	1.5 (1.09-2.08)	1.11 (0.76-1.65)	<.001
Creatinine, mmol/L	69.0 (62.0-78.5)	76.1 (68.8-89.2)	.004
Urea, mmol/L	4.75 (4.0-5.65)	4.65 (3.93-5.5)	.34
Inflammatory and asthma specific biomarkers			
White blood cell count, 10^3/μL	6.56 (5.44-7.72)	6 (5.02-7.02)	.02
C-reactive protein, mg/L	2.67 (0.58-8.0)	1.78 (0.89-2.29)	.03
Interleukin 4, pg/mL	0.005 (0.005-0.005)	0.005 (0.005-0.005)	.95
Interleukin 5, pg/mL	0.005 (0.005-0.005)	0.005 (0.005-0.005)	.44
Interleukin 6, pg/mL	0.78 (0.45-1.72)	0.56 (0.26-0.84)	.01
Interleukin 10, pg/mL	0.57 (0.26-0.99)	0.23 (0.005-0.54)	.001
Interleukin 12 (p70), pg/mL	0.005 (0.005-1.25)	0.005 (0.005-0.89)	.46
Interleukin 17A, pg/mL	0.005 (0.005-0.15)	0.005 (0.005-0.11)	.7
Interleukin 23, pg/mL	0.005 (0.005-18.18)	0.005 (0.005-17.67)	.79
Interferon γ, pg/mL	0.005 (0.005-0.31)	0.04 (0.005-0.19)	.46
A disintegrin and metalloproteinase domain-containing protein 33, ng/mL	0.86 (0.23-1.91)	0.43 (0.21-1.05)	.02
Cardiovascular parameters			
von Willebrand factor plasma activity, %	108.5 (90.9-123.4)	102.2 (91.4-119.2)	.42
Pentraxin-3, ng/mL	1.17 (0.7-1.7)	1.25 (0.25-2.24)	.78
Echocardiographic parameters			
Left ventricular diastolic diameter, cm	4.7 (4.5-4.9)	4.7 (4.5-5.0)	.49
Left ventricular systolic diameter, cm	3 (2.9-3.1)	3 (2.9-3.1)	.6
Right ventricular diameter, cm	2.2 (2.1-2.5)	2.1 (1.9-2.3)	.005
Left ventricle posterior wall thickness, cm	0.9 (0.9-1.0)	0.9 (0.8-1.0)	.13
Ejection fraction, %	67 (65-68)	68 (68-68)	<.001
Pulmonary artery pressure, mmHg	36 (34-38)	34 (32-40)	.46
Ultrasound parameters of endothelial dysfunction and atherosclerosis			
Relative increase of a flow-mediated dilatation of the brachial artery, %	7.89 (4.76-10.53)	10.26 (8.51-12.5)	<.001
Intima-media thickness of the common carotid artery, cm	0.75 (0.65-0.8)	0.65 (0.55-0.75)	<.001

[a]Categorical variables are presented as numbers (percentages), continuous variables as median and interquartile range.

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β=0.21 [95%CI, 0.04-0.38], for serum creatinine and urea, respectively).

Although a simple comparison between asthma and control individuals revealed no difference in circulating pentraxin-3 (Table 2), we found that the level was below the ELISA detection threshold in many more controls (n=16 [26%] vs n=6 [5%], *P*=0.01). Surprisingly, an analysis limited to those with detectable pentraxin-3 revealed lower levels in asthmatics (1.2 [0.87-1.84], n=84 vs 1.67 [1.18-2.5], n=42, *P*=.01 after adjustment for potential confounders). In asthma, pentraxin-3 correlated positively with IL-6 (β=0.2 [95%CI, 0.11-0.29]) and IL-10 (β=0.5 [95%CI, 0.42-0.58]), but inversely with white blood cell count (β= –0.19 [95%CI, –0.31 to –0.07]) and vWF (β=–0.17 [95%CI, –0.3 to –0.04]). Interestingly, a positive association was revealed between pentraxin-3 and airway remodeling indices, including the WAR and WTR of RB10 (β=0.2 [95%CI, 0.1-0.3] and β=0.2 [95%CI, 0.1-0.3], respectively) and LB10 (β=0.18 [95%CI, 0.05-0.31] and β=0.23 [95%CI, 0.1-0.36], respectively).

More details on laboratory test results, including their relationships with vWF activity and circulating pentraxin-3, as well as FMD% and IMT in controls are provided in the online supplement.

Ultrasound Parameters

Asthmatics had a slightly lower ejection fraction and increased right ventricular diameter (Table 2). Interestingly, in both groups, we demonstrated positive associations between circulating pentraxin-3 and left ventricular diastolic and systolic diameters (β=0.37 [95%CI, 0.21-0.53], β=0.19 [95%CI, 0.05-0.33] for asthmatics and β=0.37 [95%CI, 0.14-0.5], β=0.28 [95%CI, 0.1-0.46] for controls).

Asthmatics were characterized by 23% lower FMD% and 15% thicker IMT than controls (both *P*<.001, also after adjustment for potential confounders) (Table 2). Moreover, differences were demonstrated for all asthma severity subtypes (Figure, A and B). Asthmatics had a markedly higher risk of a lower FMD%, defined as values below the cut-off point of 8.33% (OR 3.65 [95%CI, 2.06-6.48], *P*<.0001), than the control group.

The main relationships between FMD% and demographic, echocardiographic, spirometry, and laboratory variables in asthma patients are presented in Figure, C. FMD% was unfavorably related to older age, higher BMI, severity of bronchial obstruction, increased left ventricle posterior wall thickness and right ventricular diameter, as well as

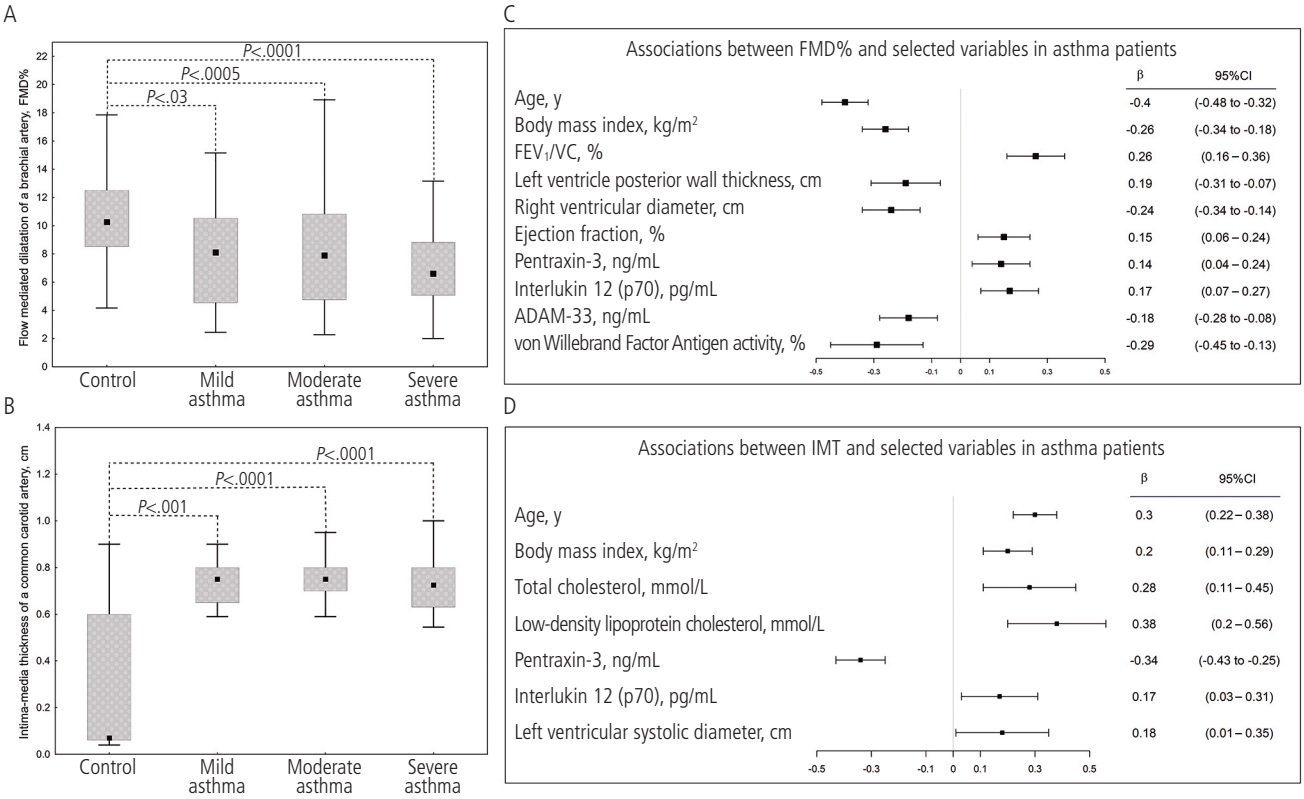

Figure. Left side: Relative increase in flow-mediated dilatation of the brachial artery (A) and intima-media thickness of the common carotid artery (B) in controls and asthma patients. Data are presented as median, interquartile range, and maximum and minimum values. The numbers on the graph represent *P* values compared with controls. Right side: Main associations between the relative increase in flow-mediated dilatation in the brachial artery (FMD%) (C) and the intima-media thickness of the common carotid artery (IMT) (D) and demographic, echocardiographic, spirometry, and laboratory parameters in asthma patients. ADAM-33 indicates a disintegrin and metalloproteinase domain-containing protein 33; FMD%, a relative increase in flow-mediated dilatation of the brachial artery; FEV_1/VC, forced expiratory volume in 1 second/vital capacity; IMT, intima-media thickness of the common carotid artery.

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higher circulating ADAM-33 and plasma vWF activity. In turn, increased ejection fraction and increased circulating pentraxin-3 and IL-12 (p70) had a favorable impact on this parameter (Figure, C). Surprisingly, higher FMD% was observed in patients receiving montelukast (9.38 [6.38-11.43] [n=11] vs 6.12 [4.65-8.82] [n=61]; *P*=.04). In turn, lower values were independently demonstrated in patients with hypertension (6 [5.76-10] [n=53] vs 9.38 [8.16-10.63] [n=39]; *P*=.001) and hypercholesterolemia (6.45 [4.76-11.29] [n=28] vs 9.28 [7.89-11.11] [n=64]; *P*=.02).

The results of a multiple regression model demonstrated that favorable higher FMD% in asthmatics was independently determined by younger age, less severe bronchial obstruction, thinner left ventricle posterior wall, and, interestingly, higher blood levels of IL-12 (p70) and pentraxin-3 (Table 3). These variables accounted for 46% of variability in FMD% in asthmatics.

Figure, D depicts the main associations between IMT and demographic, echocardiographic, and laboratory variables in asthmatics. IMT was unfavorably associated with older age, higher BMI, increased left ventricular systolic diameter, hypercholesterolemia, and raised circulating IL-12 (p70). Of note, the only inverse, and thus favorable, relationship among laboratory biomarkers was demonstrated for pentraxin-3 (Figure, D).

Table 3. Results of Multiple Linear Regression Models for Flow-Mediated Dilatation of the Brachial Artery (FMD%) and Intima-Media Thickness of the Common Carotid Artery (IMT) in Asthmatics[a]

	β (95%CI)[b]	R^2
Relative increase of a flow-mediated dilatation of the brachial artery, %		
Age, y	–0.17 (–0.28 to –0.07)	0.46
FEV_1/VC index	0.24 (0.15 to 0.34)	
Interleukin 12 (p70), pg/mL	0.3 (0.21 to 0.39)	
Posterior wall thickness, cm	–0.29 (–0.39 to –0.2)	
Pentraxin-3, ng/mL	0.17 (0.08 to 0.27)	
Adjustment statistics	F=11.4, *P*<.001	
Intima-media thickness of the common carotid artery, cm		
Age, y	0.46 (0.37 to 0.55)	0.48
Glucose, mmol/L	0.38 (0.29 to 0.47)	
Posterior wall thickness, cm	0.14 (0.05 to 0.23)	
Pentraxin-3, ng/mL	–0.1 (–0.19 to –0.02)	
Adjustment statistics	F=13.7, *P*<.001	

Abbreviations: FEV_1, forced expiratory volume in 1 second; VC, vital capacity.
[a]The variables shown were documented as independent determinants of both the study parameters, explaining 46% and 48% of variability in FMD and IMT, respectively.
[b]The resulting standardized regression coefficient (β) with 95% confidence interval (95%CI) for a factor (independent variable) indicates the increase/decrease in the SDs of the dependent variable (FMD% or IMT) when that particular factor increases by 1 SD and all other variables in the model remain unchanged.

Higher IMTs were independently documented in asthmatics with hypertension (0.72 [0.6-0.8] [n=53] vs 0.7 [0.6-0.75] [n=39]; *P*=.04) and in diabetes mellitus (0.75 [0.7-0.83] [n=18] vs 0.7 [0.6-0.8] [n=74]; *P*=.02) and in those receiving statins (0.8 [0.75-0.8] [n=22] vs 0.7 [0.6-0.8] [n=70]; *P*=.03).

A multiple regression model built for IMT in asthmatics demonstrated that higher IMT was independently determined by older age, raised serum glucose, thicker left ventricle posterior wall, and lower serum pentraxin-3 (Table 3). These parameters accounted for 48% of the variability in IMT.

Discussion

In the present study, we showed that asthma is characterized by endothelial dysfunction (decreased FMD%) and an increased risk of accelerated atherosclerosis (thicker IMT of the common carotid artery). As expected, an unfavorable lower FMD% was documented in patients with hypercholesterolemia and hypertension, as well as in those who were older and had higher BMI. Impaired endothelial function of the brachial artery was related to higher levels of circulating ADAM-33, an asthma-specific biomarker, and the plasma activity of vWF, which was in turn positively associated with renal parameters, even if they were in the normal range. This interesting finding points to parallel alterations in kidney vessels and renal function, which took the form of slightly higher concentrations of urea and creatinine in the blood. Chronic kidney disease and cardiovascular disease have been shown to share risk factors, and endothelial function is significantly impaired in end-stage renal disease [34]. Our results are consistent with these observations, although, once again, they demonstrate that major cardiovascular risk factors (eg, arterial hypertension, hypercholesterolemia, obesity, and diabetes mellitus) might aggravate atherosclerosis, partly by impairing vessel endothelial cell function [14,35].

To date, few papers have addressed endothelial dysfunction in asthmatics, although their results are consistent with ours [15-19]. Compared with matched healthy individuals, children with asthma present with increased IMT [15,16] and diminished FMD% in the brachial artery [15]. In addition, studies performed in adult asthma patients have demonstrated increased brachial-ankle pulse wave velocity [18], thickening of IMT [8], presence of atherosclerotic plaques in carotid arteries [19], and decreased FMD% [36]. However, the aforementioned studies were performed in small groups. In contrast, we analyzed more than 90 asthmatics with a range of asthma severity scores. To our knowledge, this is the largest asthma group in which endothelial dysfunction has been addressed. Particularly interesting in our study is the inverse correlation between FMD% and severity of bronchial obstruction. This is the first time such a relationship has been revealed in asthmatics. Our findings could indicate that more severe asthma, in the form of poorer lung function, is related to impaired endothelial function; hence the increased risk of atherosclerosis. A similar conclusion may also be drawn from our previous study, where we reported a positive association between lung function and plasma vWF activity, which is a well-established marker of endothelial cell activation [37].

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Our results in that context mirror epidemiological studies that provide further evidence for the relationship between impaired lung function and cardiovascular outcomes, including heart failure, stroke, and coronary artery disease [38-41]. Moreover, we also demonstrated correlations between higher FMD%, thinner heart walls, and better ejection fraction, thus supporting the hypothesis that healthier endothelium improves the whole cardiovascular system and protects against heart failure [42].

To our knowledge, pentraxin-3 has not been comprehensively studied in asthma patients. We found that this inflammatory protein was more frequently above the ELISA detection point in asthmatics. However, the analysis limited to those with detectable circulating pentraxin-3 revealed, surprisingly, that levels were higher in controls. This interesting finding warrants a comment. Pentraxin-3 has become a novel and sensitive marker of endothelial activation, which is associated with peripheral artery disease, myocardial infarction, unstable angina pectoris, atherosclerosis, and heart failure [27]. Indeed, we observed that not only was circulating pentraxin-3 correlated with selected inflammatory biomarkers in asthmatics, but that it was also related to better endothelial function in patients and controls, thinner IMT, and lower plasma vWF activity in asthma, thus suggesting its protective function in vessel endothelium. Animal models also provide increasing evidence for the immunomodulatory role of pentraxin-3 in cardiovascular outcomes and atherosclerosis. Lack of pentraxin-3 in double-knockout mice makes them susceptible to atherosclerosis via greater accumulation of macrophages and higher expression of adhesion molecules in the vascular wall [43]. Salio et al [44] reported increased heart damage and greater inflammatory response after ligation of the coronary artery in pentraxin-3–deficient mice. Pentraxin-3 also played a protective role in arterial thrombosis by inhibiting the prothrombotic effects of fibrinogen and collagen [45]. In conclusion, pentraxin-3 is consistently related to cardiovascular disease, although its exact function remains unclear.

In our study, it was noteworthy that CT revealed pentraxin-3 to be unfavorably related to lung airway remodeling. It has been demonstrated that pentraxin-3 might be raised in the sputum of children with asthma and that this increase correlates well with bronchial obstruction [46]. Moreover, Zhang et al [47] reported higher expression of pentraxin-3 in airway smooth muscle cells in asthma patients and hypothesized that it could have an effect on airway remodeling. Our data are consistent with this observation, indicating a possible contribution of pentraxin-3 to asthma remodeling. Also interesting in this context is the inverse relationship between FMD% and ADAM-33, which is overexpressed in the epithelium and airway smooth muscle cells of asthma patients, thus promoting angiogenesis and cell proliferation and, potentially, airway remodelling [48]. However, this relationship might also suggest that ADAM-33 is directly involved in endothelial cell function through its complex structure and function, or by local lung release of other contributors to endothelial damage [49].

Of note, we observed a favorably higher FMD% in asthma patients treated with montelukast, a leukotriene receptor antagonist. Leukotrienes are potent proinflammatory modulators that play a key role in the pathogenesis of asthma. Emerging data indicate that they are also active in atherosclerotic plaque and contribute to atherosclerosis and cardiovascular conditions [50]. It cannot be excluded that these very well-tolerated medications, which are currently used in asthma therapy, may come to play a key role in the treatment of atherosclerosis, although large experimental and observational studies are needed to verify this hypothesis.

Our study is subject to a series of limitations. First, the patient and control groups were relatively small. Second, the patients were relatively old, and most had moderate-to-severe asthma. Third, since we measured each laboratory variable at a single time point, we cannot exclude changes over time. Fourth, the statistical associations reported here may not necessarily indicate cause-effect relationships. In vitro models are needed to elucidate the role of pentraxin-3 in the pathogenesis of asthma, endothelial dysfunction, and the development of atherosclerosis. Finally, the clinical relevance of the relationships we demonstrated, particularly in terms of vascular outcomes and asthma remodeling, remains to be established.

Conclusions

In summary, our study demonstrates that asthma is characterized by endothelial dysfunction that can be noninvasively monitored in terms of FMD% via a simple ultrasonographic test. Impaired endothelial function was related to airway obstruction and blood levels of ADAM-33, an asthma-specific biomarker. Although atherosclerosis is regulated by a complex mechanistic pattern, our data suggest that classic cardiovascular risk factors, including hypercholesterolemia, arterial hypertension, diabetes, and obesity, need to be more comprehensively controlled by lifestyle changes and/or medications in asthmatics, particularly in those with severe disease. The biological role of pentraxin-3 is unknown, although our data suggest that it can protect against endothelial dysfunction. Pentraxin-3 might also be involved in airway remodeling.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Methods

Inclusion and exclusion criteria

Severity of asthma was categorized according to the Global Initiative for Asthma (GINA) (1) guidelines."Mild" asthma was defined as mild disease, treated with low daily dose of inhaled corticosteroids (ICS) (<250 μg of fluticasone propionate [FP] [dry powder inhaler] or equivalent) and/or short acting β_2-agonists on demand. "Moderate" asthma was defined as mild persistent disease treated with low (combined with long-acting β_2-agonists) or medium dose of ICS (250-500 μg of FP or equivalent). "Severe" asthma was defined as asthma that requires high dose of ICS (>500 μg of FP or equivalent) with long-acting β_2-agonist to prevent it from becoming uncontrolled or asthma that remains poorly controlled despite that treatment.

Arterial hypertension was defined based on a history of hypertension (blood pressure >140/90 mmHg), or administration of antihypertensive treatment. Hypercholesterolemia was defined as the previously diagnosed and treated with statins, or serum total cholesterol >5.2 mmol/l. Diabetes mellitus was defined as the current use of insulin, or oral hypoglycemic medications, or fasting serum glucose >7.0 mmol/l. Congestive heart failure was defined as the left ventricular ejection fraction below 40%. Coronary heart disease was defined as a clinical manifestation of angina pectoris or myocardial infarct in the past. Liver injury was defined as the liver enzymes above the upper limit of the reference range.

Ultrasound examinations

Flow-mediated dilatation (FMD) of the right brachial artery was assessed using Celermayer' method (2), as described previously (3,4). A baseline sagittal diameter (D1) of a

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distal part of the brachial artery was measured in the M-presentation by using a 10 MHz linear array ultrasonic transducer placed 2-3 cm proximal to the arterial bifurcation. A sphygmomanometer cuff was then placed on the forearm below the elbow and inflated to a pressure of 200 mmHg for 5 minutes and released. One minute after releasing the cuff, the brachial artery diameter was measured again (D2) at the same point. FMD was defined as the increase of brachial artery diameter after deflation of the cuff and was expressed as a percentage of the baseline diameter (FMD %= [(D2-D1)/D1] x 100%).

The intima-media thickness (IMT) of the common carotid artery was measured by ultrasound with a 10 MHz linear transducer. The thickness of the anterior and posterior walls were assessed bilaterally in the longitudinal projection immediately before they bifurcate. The mean value of the both sidesmeasurements was used in further analysis (3,4).

Postbronchodilator spirometry

Postbronchodilator spirometry (after 400 μg of albuterol) was made according to the American Thoracic Society standards (5), using a Jaeger MasterLabspirometer (Jaeger-Toennies GmbH, Hochberg, Germany).

Lung computed tomography (CT)

Lung CT was performed 1 hour after administration of inhaled albuterol (400 μg), using 64-raw multidetector computed tomography (Aquilion TSX-101A, Toshiba Medical Systems Corporation, Otawara, Japan), without administration of intravenous contrast medium, in a helical scanning mode, with CT parameters: 64 x 0.5 mm collimation, helical pitch of 53 and 0.5 second per rotation with standard radiation dose [150±50 mAs and 120 kVp]). Patients were scanned in the supine position at maximal inspiration with the arms held over the head.

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Results

Levels of interleukin (IL)-4 and IL-5 were below the detection point in almost allsubjects, while IL-6 was detectable in the majority of analyzed samples. Concentrations of IL-10 were measurable in about 14% of asthmatics and 27% of controls, while IL-12(p70), IL-17A, IL-23, and interferon gamma (INFγ) were above the detection threshold in about 60% and 35% of asthma and control individuals, respectively.

In asthmatics activity of von Willebrand factor (vWF) remained in positive associations with inflammatory markers, including C-reactive protein (CRP) (β=0.35 [95%CI: 0.03-0.23]), IL-6 (β=0.1 [95%CI: 0.01-0.19]), IL-10 (β=0.27 [95%CI: 0.17-0.37]), IL-17A (β=0.13 [95%CI: 0.03-0.23]), and ADAM-33 (β=0.22 [95%CI: 0.12-0.32]). In patient group vWF was higher in those with diabetes (119.3 [111.2-125], n=18 vs. 103.2 [89.9-120.3], n=74, p=0.007), hypercholesterolemia (117.4 [99.9-124.8], n=28 vs. 101.2 [86.7-115], n=64, p=0.003), deep vein thrombosis in medical history (127 [111.1- 134.8], n=9 vs. 104.6 [90.4-118.7], n=83, p=0.003), and treated with oral corticosteroids (124.3 [105.3-133.2], n=23 vs. 103.3 [89.9-119.7], n=69, p=0.004).

In controls, similarly to asthma patients, FMD% was inversely related to the age (β=-0.4 [95%CI: -0.53 to -0.27]) and body mass index (BMI) (β=-0.23 [95%CI: -0.38 to -0.08]). Among laboratory variables the onlypositive association was demonstrated with circulating pentraxin-3 (β= 0.23 [95%CI: 0.03-0.43]) and the only negative with vWF activity (β=-0.24 [95%CI: -0.37 to -0.11]). In turn, IMT in this group of subjects was positively related to the age only (β=0.26 [95%CI: 0.12-0.4]). Moreover, in controls IMT remained in relationships with selected echocardiographic parameters, including interventricular septum thickness (β=0.2 [95%CI: 0.02-0.38]), posterior wall thickness (β=0.19 [95%CI: 0.01-0.37]), right ventricle diameter (β=0.37 [95%CI: 0.17-0.57]), and ejection fraction (β=-0.2 [95%CI: -0.36

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to -0.04]). Among laboratory variables in controls IMT correlated with triglycerides (β=0.17 [95%CI: 0.01-0.33]) and high-density lipoproteins (β=-0.35 [95%CI: -0.49 to -0.21]).

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Table 1S. Selected basic laboratory tests results and lung computer tomography indices of airway remodeling in asthmatics.

	Patients n=92	Controls n=62	p-value
Basic laboratory tests			
Hemoglobin, g/dl	13.5 (12.9-14.4)	13.7 (12.6-15)	0.4
Red blood cells, 10^6/μl	4.62 (4.32-4.9)	4.51 (4.18-4.85)	0.14
Blood eosinophilia, 10^3/μl	210 (110-400)	140 (110-200)	0.1
Glucose, mmol/l	5.00 (4.70-5.40)	4.98 (4.76-5.20)	0.24
Alanine transaminase, IU/l	26 (21-37.5)	21.5 (15-29)	0.006
Aspartate transaminase, IU/l	23 (21-37.5)	21.5 (17-25)	0.04
Lung computed tomography airway remodeling indices			
Right lower lobe basal posterior bronchus wall thickness, mm	1.8 (1.6-2.1)	-	-
Right lower lobe basal posterior bronchus wall area ratio	72.15 (67.9-76.2)	-	-
Right lower lobe basal posterior bronchus wall thickness ratio	23.5 (21.4-25.6)	-	-
Left lower lobe basal posterior bronchus wall thickness, mm	1.9 (1.7-2.2)	-	-
Left lower lobe basal posterior bronchus wall area ratio	72.3 (68.1-75.4)	-	-
Left lower lobe basal posterior bronchus wall thickness ratio	23.6 (21.8-25)	-	-

Data is presented as median and interquartile range.

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