

Allergic Rhinitis, Asthma, and Atherosclerosis in the Bruneck and ARMY Studies

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Background: Several diseases characterized by chronic inflammation and immune activation have been linked to enhanced risk for atherosclerosis. The potential association between allergies and atherosclerosis, however, remains to be defined.

Methods: The association between common allergic diseases (allergic rhinitis and asthma) and 5-year development and progression of carotid atherosclerosis (Bruneck Study) and high intima-media thickness in carotid and femoral arteries (Atherosclerosis Risk Factors in Male Youngsters [ARMY] study) was investigated. The Bruneck Study is a prospective population-based survey of 826 men and women aged 40 to 70 years; the ARMY study is a cross-sectional evaluation of 141 men aged 17 or 18 years.

Results: Subjects with allergic disorders were at a significantly increased risk for high intima-media thickness in the ARMY study (odds ratio, 2.5; 95% confidence interval, 1.1-5.5; $P=.03$) and for atherosclerosis

development and progression in the Bruneck Study (odds ratio, 3.8; 95% confidence interval, 1.4-10.2; $P=.007$). The associations remained significant after multivariate adjustment for a broad array of established and potential vascular risk factors. When IgE levels were substituted for the clinical allergy variable, findings were confirmed in the Bruneck Study (adjusted odds ratio, 1.7; 95% confidence interval, 1.1-8.0), for a 1-SD increase in IgE level ($P=.02$).

Conclusions: This study documents enhanced atherosclerosis among subjects with common allergic diseases. Our findings fit well with the emerging concept that key components of allergies, such as leukotrienes or mast cells, are active in human atherogenesis and further extend the growing list of immune system-mediated and chronic inflammatory disorders that have been linked with enhanced risk for atherosclerosis.

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DURING THE PAST YEARS, evidence has accumulated that inflammatory processes and the immune system are crucially involved in human atherogenesis.^{1,2} In many diseases characterized by immune system activation and chronic inflammation, such as systemic lupus erythematosus, rheumatoid arthritis, and chronic infections,^{1,3} accelerated development and enhanced risk for atherosclerosis are firmly established. In addition, allergic disorders such as allergic rhinitis or asthma may also contribute to enhanced risk for atherosclerosis.⁴ Indirect support for this clinically relevant concept is derived from previous studies showing that laboratory surrogates of allergic disorders, such as IgE levels,⁵⁻⁷ eosinophilia,⁸ positive skin prick test results,⁸ daily pollen burden,⁹ measurements of lung function,^{10,11} and self-reported asthma,^{12,13} are associated with increased risk for cardiovascular diseases and death. However, there are few data to directly support a role for allergies in atherogenesis in human

beings. Recently, a cross-link between asthma and atherosclerosis has received attention, given the finding that polymorphisms in the 5-lipoxygenase and 5-lipoxygenase-activating protein genes, 2 key genes in the regulation of leukotriene synthesis, predict a high risk for atherosclerosis and its main clinical sequelae, stroke and myocardial infarction.¹⁴⁻¹⁶ In addition, there is increasing awareness that the cellular hallmark of asthma, the mast cell, is a frequent constituent of the diseased vessel wall and an active contributor to atherogenesis¹⁷ (**Figure**).

METHODS

STUDY SUBJECTS

The Bruneck Study was a prospective population-based survey of the epidemiology and pathogenesis of atherosclerosis.^{2,18-21} At the 1990 baseline evaluation, the study population was recruited as a random sample of all inhabitants of Bruneck (Province of Bolzano), Italy, stratified for sex and age. One thousand subjects were randomly selected, 125 women and

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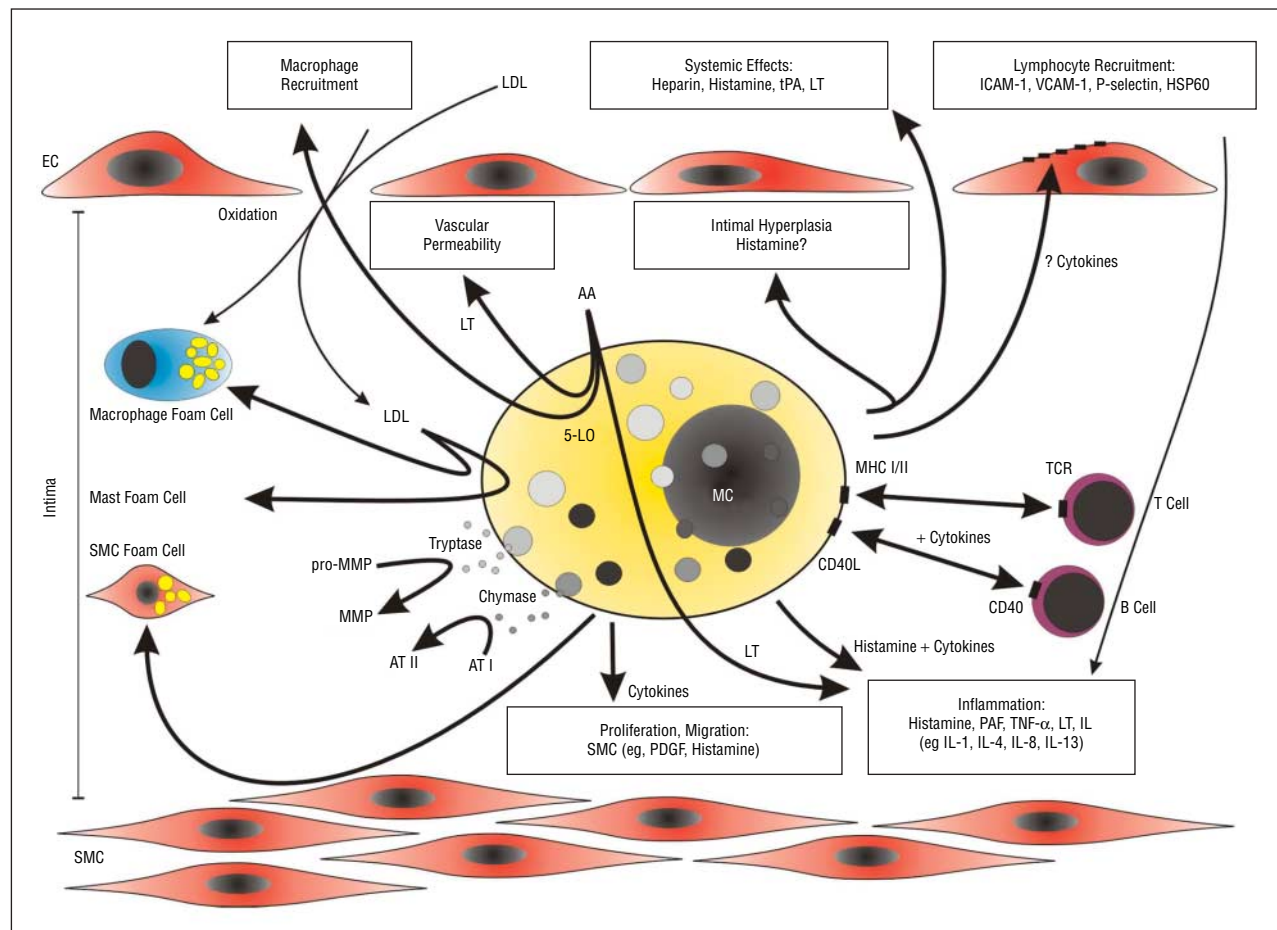


Figure. Potential pathogenic role of mast cells in atherogenesis. AA indicates arachidonic acid; AT, angiotensin; CD40L, CD40 ligand; EC, endothelial cell; HSP60, heat shock protein 60; ICAM, intercellular adhesion molecule; IL, interleukin; LDL, low-density lipoprotein cholesterol; 5-LO, 5-lipoxygenase; LT, leukotriene; MC, mast cell; MHC, major histocompatibility complex; MMP, matrix metalloproteinases; PAF, platelet-activating factor; PDGF, platelet-derived growth factor; SMC, smooth muscle cell; TCR, T-cell receptor; TNF- α , tumor necrosis factor α ; tPA, tissue plasminogen activator; and VCAM, vascular cell adhesion molecule.

125 men in each of the fifth to eighth decades of life. Of these, 936 subjects participated, and data assessment was completed in 919 subjects. All participants were white. Between 1990 and reevaluation in 1995, 63 subjects died or moved from the area. Among the remainder, ultrasonographic follow-up in 1995 was complete in 826 subjects (96.5%). Data presented herein pertain to the follow-up period between 1990 and 1995.

The Atherosclerosis Risk Factors in Male Youngsters (ARMY) study was performed in Innsbruck, Austria. In brief, every male citizen in Austria undergoes a thorough physical examination to assess physical fitness for recruitment into the Austrian army in the year he is 18 years old, except for those with chronic diseases or permanent disabilities. In the study period between January and June 2001, the first 6 volunteers among those who registered at the recruiting office in Innsbruck on randomly selected Mondays or Tuesdays were included in our study. A total of 159 subjects agreed to participate. Data assessment was incomplete for 18 participants, which left data for 141 subjects for the current analysis. Both studies were approved by the appropriate ethics committees, and all study subjects gave their written informed consent.

CLINICAL HISTORY AND EXAMINATION

The participants of both studies underwent a thorough clinical examination and completed the same standardized questionnaires about current and past exposure to vascular risk fac-

tors.^{20,22} Body mass index (calculated as weight in kilograms divided by the square of height in meters) was calculated, and smoking status and alcohol consumption were recorded as detailed previously.^{20,22,23} Hypertension was defined as blood pressure of 140/90 mm Hg or greater (mean of 3 independent measurements obtained with a standard mercury sphygmomanometer after at least 10 minutes of rest) or use of antihypertensive drugs.

In the Bruneck Study, the diagnosis of asthma was established by means of a 3-step procedure: (1) As part of the study protocol, we assessed a detailed medical and medication history, and all participants underwent a thorough physical examination and standard lung function tests. (2) If this screening revealed symptoms or clinical signs suggestive of asthma, subjects were referred to a specialist in pulmonary diseases for further evaluation. The specialist confirmed or ruled out the diagnosis of asthma, thereby adhering to standard diagnostic guidelines. (3) The Bruneck Study team collected the information provided by the specialist and made an appropriate coding. If asthma had been diagnosed in any subject before study enrollment and detailed records were available, step 2 was omitted. In the ARMY study, subjects in whom asthma had been diagnosed were excluded from the military recruitment examination and, thus, were unavailable for enrollment. Two subjects had symptoms suggestive of asthma, and the diagnosis was confirmed by a specialist in pulmonary diseases.

Allergic rhinitis was assessed using a questionnaire similar to one standardized and validated by the PRAGMA (Pro-

gramme de Recherches Appliquées à la Gestion des Maladies Allergiques) group.^{24,25} The skin prick test or radioallergosorbent test for specific allergens was not performed as part of the study protocol; however, results of such tests if performed before study enrollment were carefully collected and available for 15 subjects in the ARMY study. No test results were available for subjects in the Bruneck Study.

LABORATORY ANALYSIS

All blood samples were drawn after subjects had fasted overnight. Laboratory values were assessed with standard procedures as detailed previously.²⁰ In the Bruneck Study, IgE levels were assessed with latex-enhanced nephelometry (Dade Behring, Marburg, Germany). In the ARMY study, a standard fluorescent enzyme immunoassay (UniCAP; Pharmacia Diagnostics, Uppsala, Sweden) was used. Cellular and humoral immune reaction to human and mycobacterial heat shock protein 60 was estimated with a peripheral blood mononuclear cell proliferation assay and enzyme-linked immunosorbent assays as detailed previously.^{21,22}

ASSESSMENT OF ATHEROSCLEROSIS

In the Bruneck Study, the ultrasonographic protocol involves scanning the internal carotid artery (bulbous and distal segments) and the common carotid artery (proximal and distal segments) on either side with a 10-MHz imaging probe (ATL8; ATL Ultrasound, Bothell, Wash). Atherosclerotic lesions were defined according to 2 ultrasonographic criteria: wall surface (protrusion or roughness of the arterial boundary) and wall texture (echogenicity). The maximum axial diameters of plaques were measured in each vessel segment. Development and progression of atherosclerosis was defined as the presence of new plaques in previously normal vessel segments or a relative increase in the maximum diameter of preexisting plaques exceeding twice the measurement error of the method. Details of the variability of the ultrasonographic methods have been extensively described previously.^{18,19}

In the ARMY study, the ultrasonographic protocol involved scanning of the internal carotid artery, carotid bulb, common carotid artery, and superficial femoral artery on both sides with a 10-MHz broadband linear transducer (HDI 3000; ATL Ultrasound). All scanning was performed by the same sonographer using different scanning angles (anterior and posterolateral) to identify the greatest wall thickness. Longitudinal images directed through the center of the artery were taken at each vessel site. Measurements were made from stored digital images by an experienced reader (J.W.). The intima-media thickness (IMT) was assessed at the far wall as the distance between the interface of the lumen and the intima and the interface between the media and the adventitia. The maximal IMT was recorded at each of 4 vessel segments and averaged for the left and right sides. High IMT was present when at least 1 segment-specific IMT exceeded the 90th percentile. The outcome categories in both studies were highly reproducible (κ coefficient >0.8) in a sample of 100 subjects with 2 independent assessments of atherosclerosis and IMT.

STATISTICAL ANALYSIS

The associations of allergic disorders and IgE with atherosclerosis development and progression in the Bruneck Study and high IMT in the ARMY study were tested by means of logistic regression analysis, with the test procedure determined by the maximum likelihood estimators. Base models were adjusted for age and sex in the Bruneck Study and were unadjusted in the

ARMY study. Multiple logistic regression analyses were controlled for fixed standard sets of established and potential vascular risk factors as established in previous analyses.²⁰ In the Bruneck Study, vascular risk factors included age, sex, high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol level, hypertension, pack-years of smoking, ferritin concentration, leukocyte count, alcohol consumption, lipoprotein(a) level, microalbuminuria, hypothyroidism, and baseline atherosclerosis; in the ARMY study, vascular risk factors included diastolic blood pressure (continuous variable), smoking, alcohol consumption, high-density lipoprotein cholesterol level, cellular and humoral reactivity against heat shock protein 60, and pulmonary function (maximum expiratory flow at 50% of vital capacity). All of these variables have previously been shown to be significantly associated with the risk for atherosclerosis development and progression (Bruneck Study) and high IMT (ARMY study); for further details, see Willeit et al²⁰ and Knoflach et al.²² Analysis and the way of risk factor adjustment were strictly prespecified to avert multiple testings and inflation of type I error. The IgE level was treated as a continuous variable, and odds ratios (ORs) were computed for a 1-SD increase in variable levels. Findings are similar when IgE levels were ln-transformed. Calculations were performed using SPSS version 11.5 (SPSS Inc, Chicago, Ill) and BMDP (SAS Institute Inc, Cary, NC) software packages. A 2-sided *P* value less than .05 was statistically significant.

RESULTS

In the Bruneck Study, allergic rhinitis or asthma was diagnosed in 32 subjects (3.9%). In detail, 12 men and women (1.5%) had allergic rhinitis, 11 (1.3%) had asthma, and 9 (1.1%) had both allergic rhinitis and asthma. Accordingly, prevalence for allergic rhinitis was 2.6% and for asthma it was 2.4%, which corresponded well with results from a previous evaluation in elderly subjects in Switzerland.²⁶ In the ARMY study, 34 young men (24.1%) had allergic rhinitis, and 2 of these also had asthma. Clinical characteristics of the study populations are summarized in **Table 1**. Subjects with allergic disorders were at a significantly increased risk for high IMT in the ARMY study and for atherosclerosis development and progression in the Bruneck Study (**Table 2**). Base models in the ARMY study were unadjusted and in the Bruneck Study were adjusted for age and sex (Table 2). A sequential addition to the base models of variables for smoking and hypertension resulted in changes in the ORs from 3.8 to 3.9 and 4.3, respectively, in the Bruneck Study and from 2.5 to 2.5 and 2.7, respectively, in the ARMY study. All associations remained significant after multivariate adjustment for a broad array of established and potential vascular risk factors (multivariate ORs, 3.9 [*P* = .02] and 3.0 [*P* = .03], respectively; Table 2). When the analysis was adjusted for systolic blood pressure or diastolic blood pressure (continuous variable) instead of hypertension, multivariate ORs were almost identical: 3.8 (95% confidence interval, 1.3-11.2) and 3.8 (95% confidence interval, 1.3-11.1), respectively.

Pulmonary function as estimated by the maximum expiratory flow at 50% of vital capacity was an independent inverse predictor of high IMT in the ARMY study²² and was adjusted for in the multivariate analysis. In the Bruneck Study, risk estimates were similar for subjects

Table 1. Clinical Characteristics of Study Subjects According to Presence or Absence of 5-Year Development and Progression of Carotid Arteriosclerosis (Bruneck Study) or Increased Intima-Media Thickness (ARMY Study)

Variable*	Bruneck Study		ARMY Study	
	No AS ^{††} (n = 436)	AS ^{††} (n = 390)	Low IMT (n = 100)	High IMT (n = 41)
Age, y	52.8 ± 9.51	63.7 ± 9.95	17.8 ± 0.7	17.8 ± 0.3
Female sex, No. (%)	248 (56.9)	164 (42.1)	0	0
BMI	24.9 ± 3.58	25.1 ± 3.9	22.4 ± 3.5	22.7 ± 4.6
Obesity, No. (%)	194 (44.5)	195 (50.0)	17 (17.0)	7 (17.1)
LDL-C level, mg/dL	133.0 ± 34.8	145.4 ± 41.0	87.8 ± 25.5	111.4 ± 25.1
HDL-C level, mg/dL	57.6 ± 13.2	54.9 ± 13.9	38.7 ± 12.4	34.4 ± 10.0
Lp(a) level, g/L	0.10 ± 0.17	0.17 ± 0.20	NA	NA
Blood pressure, mm Hg				
Systolic	139.1 ± 18.4	151.2 ± 22.2	117.3 ± 10.5	117.3 ± 10.0
Diastolic	87.5 ± 9.46	90.4 ± 10.6	77.0 ± 8.1	78.6 ± 8.1
Hypertension, No. (%)	82 (18.8)	162 (41.5)	10 (10.0)	5 (12.2)
Smoking, No. (%)	92 (21.1)	107 (27.4)	48 (48.0)	29 (70.7)
Pack-years	4.60 ± 10.3	9.03 ± 17.0	NA	NA
Alcohol consumption, mean, g/d,				
1-50	154 (35.3)	90 (23.1)	82 (82.0)	36 (87.8)
51-99	42 (9.6)	74 (19.0)	3 (3.0)	1 (2.4)
≥100	15 (3.4)	45 (11.5)	0	0
Mean ± SD	27.2 ± 33.7	20.4 ± 28.0	15.1 ± 15.6	12.9 ± 12.2
Diabetes mellitus, No. (%)	14 (3.2)	44 (11.3)	0	0
Microalbuminuria, g/L	0.016 ± 0.03	0.060 ± 0.26	0.008 ± 0.04	0.018 ± 0.05
Ferritin concentration, ng/mL	1114 ± 1161	1875 ± 1993	403 ± 286	428 ± 229
Hypothyroidism, No. (%)	23 (5.3)	36 (9.2)	NA	NA
Anti-mHSP60-antibody titer	2.9 ± 1.4	3.3 ± 1.4	1.9 ± 1.0	2.2 ± 1.0
hHSP60 stimulation index	NA	NA	2.6 ± 4.3	4.8 ± 6.6
MEF ₅₀ , L/s	NA	NA	6.2 ± 1.3	5.5 ± 1.2
AS score, mm	0.4 ± 1.3	3.4 ± 4.4	NA	NA

Abbreviations: ARMY, Atherosclerosis Risk Factors in Male Youngsters; AS, arteriosclerosis; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HDL-C, high-density lipoprotein cholesterol; hHSP60, human heat shock protein 60; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MEF₅₀, maximum expiratory flow at 50% of vital capacity during spirometry; mHSP60, mycobacterial heat shock protein 60; NA, data not available.

SI conversion factors: To convert HDL-C and LDL-C to millimoles per liter, multiply by 0.0259.

*Data are given as mean ± SD unless otherwise indicated.

†Five-year development and progression of carotid arteriosclerosis.

with isolated allergic rhinitis (n=12) and those with asthma with or without allergic rhinitis (n=20): multivariate ORs 3.0 (P=.09) and 5.3 (P=.04), respectively. In the ARMY study, in 15 of the 34 young men with allergic diseases a skin prick test or radioallergosorbent test had been performed and a specific allergen had been identified, whereas in 19 subjects no test results were available. Both groups were at similar risk for high IMT: multivariate ORs, 2.2 (P=.17) and 3.2 (P=.12), respectively. Finally, when IgE levels were substituted for the clinical allergy variable in the multivariate risk model, findings were confirmed in the Bruneck Study (Table 2).

COMMENT

Our study demonstrates a significant association between atherosclerosis and the common allergic diseases asthma and allergic rhinitis in 2 independent population samples, one consisting of young men (aged 17 and 18 years) and the other of middle-aged and elderly men and women.^{20,22} The Bruneck and ARMY studies both offer high-quality data, and the design of the Bruneck Study was prospective. In the Bruneck Study, analyses that fo-

cused on total IgE level, a laboratory surrogate of allergy, yielded confirmatory results. Lack of an association between IgE level and high IMT in the ARMY study may simply be a matter of smaller sample size or reflect the clear preponderance of seasonal allergic rhinitis in this population. It must be considered that blood samples were obtained during a period of low-allergen exposure, when IgE levels are lower than after allergen exposure, and thus differences may be less prominent.

Our findings fit well with those of previous evaluations that demonstrated associations between laboratory surrogate markers of allergies and cardiovascular disease risk.⁶⁻⁸ In a recent prospective study,¹² women but not men with self-reported physician-diagnosed asthma were at modestly increased risk for coronary heart disease (OR, 1.22; 95% confidence interval, 1.14-1.31). The more prominent association in our study may have resulted because we did not study clinical end points but focused on atherosclerosis as quantified with high-resolution ultrasonography. However, we cannot rule out that the comparatively few subjects with allergy or that residual bias may have contributed to overestimation of the true association.

Table 2. Association of Allergies and IgE Level With Atherosclerosis in the Bruneck Study and ARMY Study

Variable	No AS Increase* (n = 436)	AS Increase* (n = 390)	Age-Adjusted and Sex-Adjusted	P Value	Multivariate OR (95% CI)† ‡	P Value
			OR (95% CI)†			
Bruneck Study (N = 826) (subjects aged 40-70 y)						
Allergic rhinitis, asthma, or both, No. (%)	7 (1.6)	25 (6.4)	3.8 (1.4-10.2)	.007	3.9 (1.3-11.5)	.02
IgE level, kU/L§	78.4	160.5	1.9 (1.3-2.8)	.001	1.7 (1.1-8.0)	.02
Variable	Low IMT¶ (n = 100)	High IMT¶ (n = 41)	Unadjusted OR (95% CI)†	P Value	Multivariate OR (95% CI)†	P Value
Army Study (N=141) (subjects aged 17-18 y)						
Allergic rhinitis, asthma, or both, No. (%)	19 (19.0)	15 (36.6)	2.5 (1.1-5.5)	.03	3.0 (1.1-7.9)	.03
IgE level, kU/L§	87.1	103.5	1.1 (0.8-1.5)	.69	1.1 (0.7-1.7)	.65

Abbreviations: ARMY, Atherosclerosis Risk Factors in Male Youngsters; AS, arteriosclerosis; CI, confidence interval; IMT, intima-media thickness; OR, odds ratio.

*Five-year development and progression of carotid arteriosclerosis.

†Odds ratio and 95% CI derived from logistic regression analysis of atherosclerosis progression (Bruneck Study) or high IMT (ARMY study) on allergy or IgE level and covariates.

‡Odds ratio adjusted for age, sex, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels, hypertension, pack-years of smoking, ferritin concentration, leukocyte count, alcohol consumption, lipoprotein(a), microalbuminuria, hypothyroidism, and baseline atherosclerosis.

§Odds ratio calculated for a 1-SD increase in IgE level (1 SD equals 219 kU/L in ARMY study and 370 kU/L in Bruneck Study). Findings were similar when 1n-transformed IgE level was used.

||Odds ratio adjusted for diastolic blood pressure, smoking, alcohol consumption, high-density lipoprotein cholesterol level, cellular and humoral reactivity against heat shock protein 60, and pulmonary function.

¶High IMT in carotid or femoral arteries.

The nature of the association observed between allergies and atherosclerosis remains speculative. Aside from the unlikely possibility that this association is owing to chance, there are at least 2 plausible interpretations. First, allergic disorders may constitute a true risk factor. There is ample evidence that localized allergic diseases elicit a systemic inflammatory response mediated by the release of vasoactive peptides and cytokines into the circulation. Endothelial cells at locations distinct from the site of allergen exposure were found to enhance adhesion molecule expression, thus facilitating leukocyte trafficking into the vessel wall and potentially promoting atherosclerosis. In addition, allergic disorders are commonly associated with respiratory infections, another potential vascular risk condition.^{2,27} Second, allergic rhinitis, asthma, and atherosclerosis may share central effector pathways and some predisposing gene variants. Mast cells (Figure) and leukotrienes, 2 hallmarks of allergy, are increasingly recognized as key factors in atherosclerosis as well. Functional variants in 5-lipoxygenase and 5-lipoxygenase activating protein that enhance leukotriene synthesis or promote inflammation confer a high risk for atherosclerotic vascular disease in human beings,^{14,15} while atherosclerosis-susceptible mice exhibit excellent protection against atherosclerosis in the case of a heterogeneous deficiency of 5-lipoxygenase.²⁸ The intriguing concept of a role for mast cells and leukotrienes in atherogenesis holds great promise for the development of new preventive measures involving leukotriene antagonists or mast cell degranulation inhibitors. There is a clear need for further studies to substantiate our clinically relevant observation of a cross-link between atherosclerosis and allergies and to further specify its pathophysiologic background.

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Announcement

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Potential authors are invited to submit a 250-word abstract outlining a controversy facing internists today, the position taken regarding this controversy (eg, "pro" or "con"), and a brief summary of arguments supporting that position. If the abstract is selected, the author will be invited to write a full-length article expanding on the abstract. The section editor will select an author for an opposing, or counterpoint, article. After peer review, the two articles will be published as a pair in the journal.

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