

Original Article

A Preliminary ^{18}F -FDG-PET/MRI Study Shows Increased Vascular Inflammation in Moderate-to-Severe Atopic Dermatitis

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What is already known about this topic? In moderate-to-severe atopic dermatitis (AD), elevated systemic immune activation is increasingly recognized, and epidemiological studies suggest increased cardiovascular risk.

What does this article add to our knowledge? This study is the first to show increased cardiovascular inflammation using fluorodeoxyglucose-positron emission tomography/magnetic resonance imaging in moderate-to-severe AD.

How does this study impact current management guidelines? This study suggests that taking into account the potential for cardiovascular inflammation may be warranted in deciding on the need to use systemic treatment.

BACKGROUND: Recent data suggest that patients with atopic dermatitis (AD) have increased systemic immune activation and cardiovascular risk. However, unlike psoriasis, evaluation of active vascular inflammation using state-of-the-art imaging is lacking in AD.

OBJECTIVE: To assess aortic and carotid vascular inflammation using ^{18}F -fluorodeoxyglucose-positron emission tomography/magnetic resonance imaging (^{18}F -FDG-PET/MRI) imaging in moderate-to-severe AD versus healthy individuals.

METHODS: A total of 27 patients with moderate-to-severe AD and 12 healthy controls were imaged using ^{18}F -FDG-PET/MRI.

Target-to-background ratio (TBR) values were calculated in multiple segments of the aorta and carotid vessels.

RESULTS: Patients with AD had elevated aortic max TBR (fold change [FCH] = 1.45, $P = .057$) versus healthy controls and significantly elevated mean TBR (FCH = 1.20; $P < .05$) in the right carotid (RC) arteries versus controls. When examining greatest focal inflammation (most diseased segment [MDS] TBR), patients with AD had higher aortic inflammation (FCH = 1.28; $P = .052$). AD clinical severity significantly correlated with C-reactive protein ($\rho = 0.60$, $P < .01$) and with RC mean TBR levels ($\rho = 0.60$, $P = .04$). Stratifying patients

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Abbreviations used

AD- Atopic dermatitis
BSA- Body surface area
CRP- C-reactive protein
CT- Computed tomography
EASI- Eczema Area Scoring Index
¹⁸F-FDG- ¹⁸F-Fluorodeoxyglucose
FCH- Fold change
MDS- Most diseased segment
MRI- Magnetic resonance imaging
PET- Positron emission tomography
ROI- Region of interest
SD- Standard deviation
SUV- Standardized uptake value
TBR- Target-to-background ratio

into moderate-to-severe and very severe AD showed greater RC mean TBR in patients with very severe AD versus controls (FCH = 1.31; $P = .02$) and versus patients with moderate/severe AD (FCH = 1.23, $P = .05$). Aortic inflammation was also significantly greater in patients with very severe AD versus controls (max TBR: FCH = 1.6, $P = .04$; MDS TBR: FCH = 1.73, $P = .03$). **CONCLUSIONS:** This preliminary study is the first that establishes greater vascular (aorta and carotid) inflammation in moderate-to-severe AD versus healthy controls. Furthermore, very severe AD showed higher inflammation than both moderate/severe patients and healthy controls. Future studies with larger patient cohorts and evaluation before and after treatment are needed to determine the extent to which vascular inflammation in AD is modifiable. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Atopic dermatitis; ¹⁸F-FDG-PET/MRI; Cardiovascular inflammation; Systemic inflammation; Aorta; Carotid arteries; Inflammatory skin disease

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, affecting more than 30 million people in the United States.¹ Although it often starts in early childhood, most patients have persistent symptoms in adulthood.^{2,3} AD often also presents with a wide range of allergic and nonallergic comorbidities, including asthma, allergic rhinoconjunctivitis, food allergies, recurrent infections, and other associations.⁴

Recent data suggest that patients with AD also have increased cardiovascular risk, with higher rates of cardiovascular disease in some populations,⁵⁻¹⁰ independent of genetic risk,⁹ similar to psoriasis, another chronic inflammatory skin disease.¹¹ Consistent with this, 48.1% of patients with severe AD without a history of cardiovascular disease showed the presence of coronary plaques, as assessed by coronary computed tomography (CT) angiography, significantly higher than healthy controls who showed a rate of 21.2%.¹²

A study investigating active vascular inflammation using state-of-the-art imaging techniques, however, is lacking. Arterial calcification, shown to be increased in AD,¹² represents a late, burnt-out stage of atherosclerosis that cannot be reversed with medication. ¹⁸F-Fluorodeoxyglucose-positron emission tomography/magnetic resonance imaging (¹⁸F-FDG-PET/MRI) imaging can directly assess vascular inflammation as a surrogate for active

atherosclerotic disease activity¹³ and has been used extensively to evaluate atherosclerosis *in vivo*.¹⁴ This approach has been applied to psoriasis (in large studies with more than 150 patients) using ¹⁸F-FDG-PET/CT, in which it has been shown that patients with psoriasis have increased aortic vascular inflammation, driven by noncalcified plaque burden,¹⁵ which improved after psoriasis-targeted treatments.¹⁶ However, thus far, ¹⁸F-FDG-PET imaging studies have not been performed in patients with AD with significant disease burden. In addition, an emerging technology for detecting vascular inflammation, ¹⁸F-FDG-PET/MRI, which has lower radiation exposure, has been successfully used in autoimmune diseases,^{17,18} but has not yet been applied to inflammatory skin conditions. Therefore, the purpose of this study was to evaluate active vascular inflammation using ¹⁸F-FDG-PET/MRI in moderate-to-severe AD versus healthy individuals. Using this technique in a preliminary case-control study of 27 patients with AD and 12 controls, we found that patients with AD had increased vascular inflammation versus healthy controls.

METHODS

Patients

Twenty-seven untreated adult patients with AD were enrolled in this case-control study. Patients provided institutional review board–approved written consent, and this study was conducted according to the Declaration of Helsinki. Inclusion criteria included AD diagnosis for at least 3 years, with body surface area (BSA) at least 10% and Eczema Area Scoring Index (EASI) greater than 16. Aside from emollients, no topical or systemic medications were used for 2 and 4 weeks, respectively, before inclusion. Exclusion criteria included weight >136 kg due to space limitation in the PET/MR scanner, history of cardiovascular disease, heart failure, uncontrolled arterial hypertension, diabetes, prediabetes, any contraindication to ¹⁸F-FDG-PET/MRI, pregnancy, and uncontrolled asthma. Smoking history, weight, systolic and diastolic blood pressure, lipid profiles, C-reactive protein (CRP), electrolytes, and hepatic function tests were collected when available. Twelve healthy adult patients with no known cardiovascular disease were included for comparison. Eligible patients were sequentially enrolled from clinic visits among those who met the inclusion criteria and consented to participate in the study.

Imaging studies

All imaging was performed on a hybrid simultaneous PET/MR system (Biograph mMR; Siemens Healthcare, Erlangen, Germany); 260 MBq of ¹⁸F-FDG was injected 90 minutes before image acquisition. Patients were required to have fasted for at least 6 hours and have serum blood glucose levels <200 mg/dL before ¹⁸F-FDG administration. PET data were acquired in 2 bed positions, first positioned over the neck to image the carotid arteries for 40 minutes (90–130 minutes after injection), and secondly over the chest to image the thoracic aorta for a further 30 minutes (130–160 minutes after injection). Simultaneously acquired anatomical MRI included, for the neck: 3D time-of-flight MR angiography, and 3D and 2D turbo spin echo, black-blood vessel wall imaging in the carotid arteries, and in the chest: 2D multislice, breath-held bright-blood imaging of the thoracic aorta. PET image reconstruction employed an iterative algorithm with a $344 \times 344 \times 127$ matrix and a 2-mm full-width-at-half-maximum Gaussian post-reconstruction filter. MR-based attenuation correction used the standard approach provided by the scanner in the neck and a specialized respiration-robust approach in the chest.¹⁹ Image analysis of PET/MRI data was performed using OsiriX MD (Pixmeo, Geneva, Switzerland). For the carotid arteries, PET images were fused with time-of-flight

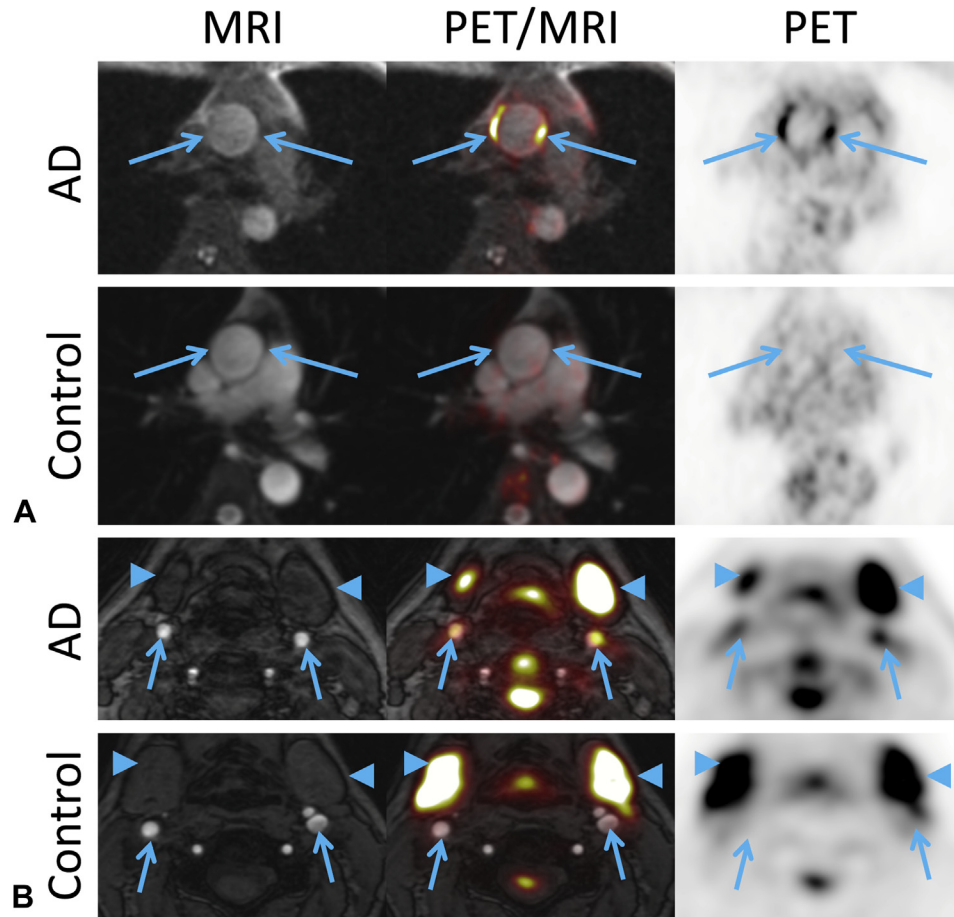


FIGURE 1. Representative MRI and PET images from patients with atopic dermatitis (AD) and normal control subjects. **A,** In the aorta, FDG-PET uptake is elevated in the ascending aorta vessel wall compared with controls (arrows). **B,** In the carotid arteries, elevated FDG-PET uptake is seen localized to the vessel wall in AD compared with controls (arrows). Intense physiological FDG-PET uptake is seen in the salivary glands (arrowhead). *FDG*, Fluorodeoxyglucose; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography.

MR-angiography images in the axial plane. On each axial slice in a volume spanning 1 cm above and below the carotid bifurcation, regions of interest (ROIs) were drawn around the carotid arteries. The left and right carotid arteries were analyzed separately. The mean and maximum standardized uptake values (SUV) of each vessel were measured for each slice. Background was measured in an ROI in the right and left jugular veins. Mean target-to-background ratio (TBR) and maximum (max) TBR were calculated by dividing the mean SUV and max SUV, respectively, by the mean SUV in the background ROI for each slice. The most diseased segment (MDS) TBR was defined as the greatest average of the max TBR for 3 adjacent slices, as previously described.²⁰ For the aorta, PET images were fused with axial 2D breath-held bright-blood images with an example image shown in Figure 1. Similar to the carotids, ROIs were drawn around the vessel wall of the ascending aorta from 2 slices above the aortic root to include the slice caudal to the inferior curve of the aortic arch, and SUVs were recorded. ROIs were then drawn in the superior vena cava and mean SUV recorded to calculate mean TBR and max TBR for each slice of the aortic bed.

Statistical analysis

Analyses were performed using R language ([R-project.org](https://www.R-project.org)) and packages available through the Bioconductor Project (www.bioconductor.org). Differences between demographic groups were

assessed using 2-side Student's *t*-test for continuous variables and the χ^2 test for categorical variables. TBR measures were normalized by log2 transformation to reduce outlier effects, and 2-sided Student's *t*-test was applied to determine significant differences between groups. Differences between groups are reported as fold change (FCH) between the geometric means of the 2 groups. Correlations were calculated using the Spearman correlation coefficient on $\log_2$ (TBR).

RESULTS

A total of 27 patients with AD and 12 healthy controls were included in this study. Demographics are included in Table I. No significant differences were found between groups in terms of age, sex, smoking, weight, high-density lipoprotein cholesterol, systolic blood pressure, and diastolic blood pressure. The AD group had a significantly higher proportion of white patients ($P = .002$) and total cholesterol ($P = .011$).

Elevated arterial inflammation found in patients with moderate-to-severe AD versus healthy controls

Using ^{18}F -FDG-PET/MRI, we calculated the TBR (a measure of vascular inflammation) in the aorta, left carotid, and right carotid of patients with moderate-to-severe AD and healthy controls. Furthermore, multiple TBR measures were used to evaluate overall

TABLE I. Demographics

Characteristic	AD (N = 27)	Control (N = 12)	P value
Age, mean (SD)	39.2 (14.3)	38.1 (11.0)	.461
Sex, n (%)			.089
Male	19 (70.1)	5 (41.7)	
Female	8 (29.9)	7 (68.3)	
Race, n (%)			.002
White	22 (75.9)	3 (25.0)	
Asian	3 (10.3)	2 (16.7)	
Black	2 (6.9)	4 (33.3)	
Other	0 (0.0)	3 (25.0)	
Smoker, n (%)			.211
Yes	3 (11.1)	0 (0.0)	
No	24 (88.9)	12 (100.0)	
Weight, mean (SD)	84.6 (19.2)	76.9 (16.5)	.212
Total cholesterol, mean (SD)	200.4 (44.5)	169.1 (21.8)	.011
HDL cholesterol, mean (SD)	51.8 (15.7)	60.1 (17.8)	.194
CRP, mean (SD)	10.3 (15.0)	N/A	N/A
Systolic BP, mean (SD)	125.2 (13.7)	124.3 (10.0)	.837
Diastolic BP, mean (SD)	79.4 (6.8)	80.1 (7.6)	.802
EASI score, mean (SD)	38.5 (13.8)	N/A	N/A
BSA, mean (SD)	66.7 (25.3)	N/A	N/A

AD, Atopic dermatitis; BP, blood pressure; BSA, body surface area; CRP, C-reactive protein; EASI, Eczema Area and Severity Index; HDL, high-density lipoprotein; SD, standard deviation.

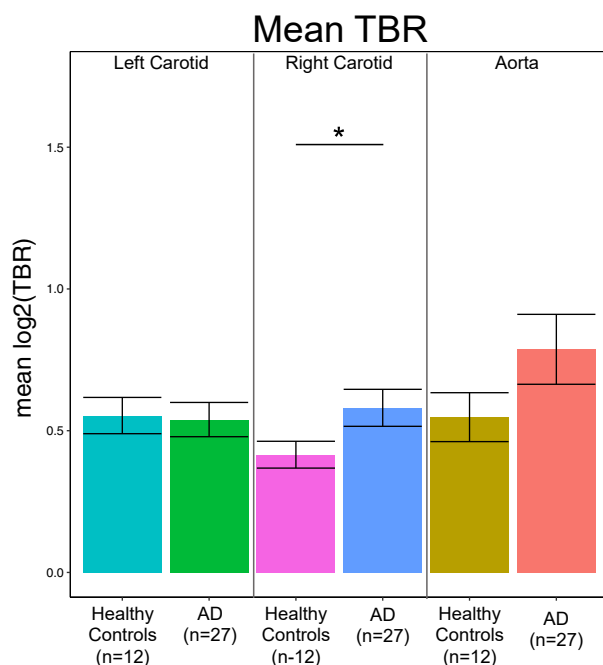


FIGURE 2. Mean target-to-background ratio (TBR) in healthy controls and patients with atopic dermatitis (AD). Mean TBR in the carotid arteries and aortas of healthy controls and patients with AD. * $P < .05$.

levels of inflammation (mean TBR), maximal levels of inflammation observed over the entire vessel (max TBR), and peak levels of inflammation found at any point along the most diseased part of the

vessel (MDS TBR; see the Methods section for details). Overall, there was a trend for increased TBR in AD compared with controls. In some comparisons of TBR measures in some vessels, the results showed statistically significant differences. We found that patients with AD had significantly elevated mean TBR versus controls in the right carotid artery ($\log_2\text{FCH} = 0.17$, $\text{FCH} = 1.12$, $P < .05$; Figure 2). Comparing max TBR between groups, inflammation was elevated in the aortas of patients with AD versus controls, approaching statistical significance ($\log_2\text{FCH} = 0.32$, $\text{FCH} = 1.24$, $P = .057$). Finally, when examining the greatest focal inflammation using the MDS TBR measure, higher aortic inflammation was found in AD ($\log_2\text{FCH} = 0.36$, $\text{FCH} = 1.28$; $P = .052$). FCHs and P values for all comparisons are listed in Table II.

Further evaluating the relationship of clinical disease severity of patients with AD with inflammatory measures, we noted that AD severity measures (EASI and BSA) significantly correlated with CRP ($\rho = 0.60$, $P < .01$ for both), confirming previous findings.²¹ Congruent with our findings of elevated inflammation in the right carotid arteries of patients with AD, we found a significant correlation of right carotid mean TBR levels with EASI ($\rho = 0.60$, $P = .04$). Max TBR and MDS TBR measures also correlated with clinical severity assessed by EASI; however, these correlations were not significant ($\rho = 0.30$, $P = .13$ and $\rho = 0.32$, $P = .11$, respectively).

As total cholesterol was elevated in the AD versus control group, we also performed a subset analysis of patients with AD and control subjects with matched total cholesterol (AD: mean 171.3, standard deviation [SD] 22.7, $n = 13$; controls: mean 169.1, SD 21.8; $P = .65$, $n = 12$). We found trends toward elevated max TBR ($\log_2\text{FCH} = 0.40$, $\text{FCH} = 1.32$; $P = .18$) and MDS TBR ($\log_2\text{FCH} = 0.43$, $\text{FCH} = 1.134$; $P = .21$) in the aortas of the AD versus healthy subjects. We also found a trend toward elevated mean TBR in the right carotid arteries for the AD group ($\log_2\text{FCH} = 0.15$, $\text{FCH} = 1.111$; $P = .37$). Furthermore, total cholesterol levels among patients with AD did not correlate with either aortic TBR or right carotid TBR (measured by mean TBR, max TBR, or MDS TBR).

More severe AD is associated with greater vascular inflammation

To further assess whether clinical severity of AD is associated with higher levels of systemic inflammation, we stratified patients into “moderate/severe AD” ($\text{EASI} \leq 50$, $n = 20$) and “very severe AD” ($\text{EASI} > 50$, $n = 7$), based on previously reported criteria.²² No differences in weight or total cholesterol were noted between these groups. Patients with very severe AD had significantly greater mean TBR than healthy controls in their right carotids ($\log_2\text{FCH} = 0.39$, $\text{FCH} = 1.31$, $P = .02$; Figure 3). Moreover, patients with very severe AD also had significantly elevated mean TBR versus patients with moderate/severe AD in their right carotids ($\log_2\text{FCH} = 0.30$, $\text{FCH} = 1.23$, $P = .05$, Figure 3). When evaluating max TBR, elevated inflammation in the right carotid of patients with very severe AD versus healthy controls and patients with very severe AD versus patients with moderate/severe AD was also found, trending to significance ($\log_2\text{FCH} = 0.40$, $\text{FCH} = 1.32$, $P = .076$ and $\log_2\text{FCH} = 0.38$, $\text{FCH} = 1.30$, $P = .067$, respectively). In the aorta, cardiovascular inflammation was also found to be significantly elevated in patients with very severe AD versus healthy controls when measured by max TBR

TABLE II. TBR comparisons

	Left carotid			Right carotid			Aorta		
	log ₂ (FCH)	FCH*	P value	log ₂ (FCH)	FCH*	P value	log ₂ (FCH)	FCH*	P value
AD (n = 27) vs Control (n = 12)									
Mean TBR	-0.01	-1.01	.873	0.17	1.12	.047 [†]	0.24	1.18	.120
Max TBR	-0.09	-1.07	.552	0.12	1.09	.251	0.32	1.24	.057 [‡]
MDS TBR	-0.14	-1.10	.467	0.12	1.09	.371	0.36	1.28	.052 [‡]
Very severe AD (n = 7) vs Control (n = 12)									
Mean TBR	0.05	1.03	.933	0.39	1.31	.016 [†]	0.54	1.45	.114
Max TBR	0.00	1.00	1.000	0.40	1.32	.074 [‡]	0.68	1.60	.044 [‡]
MDS TBR	-0.06	-1.04	.964	0.47	1.39	.106	0.79	1.73	.031 [†]
Very severe AD (n = 7) vs Moderate/severe AD (n = 20)									
Mean TBR	0.09	1.06	.782	0.30	1.23	.05 [‡]	0.40	1.32	.235
Max TBR	0.12	1.09	.766	0.38	1.30	.067 [‡]	0.49	1.40	.139
MDS TBR	0.11	1.08	.855	0.47	1.39	.072 [‡]	0.59	1.50	.097 [‡]

AD, Atopic dermatitis; FCH, fold change; TBR, target-to-background ratio.

*Positive FCH represents greater value in the first group, and negative FCH represents lower value in the first group.

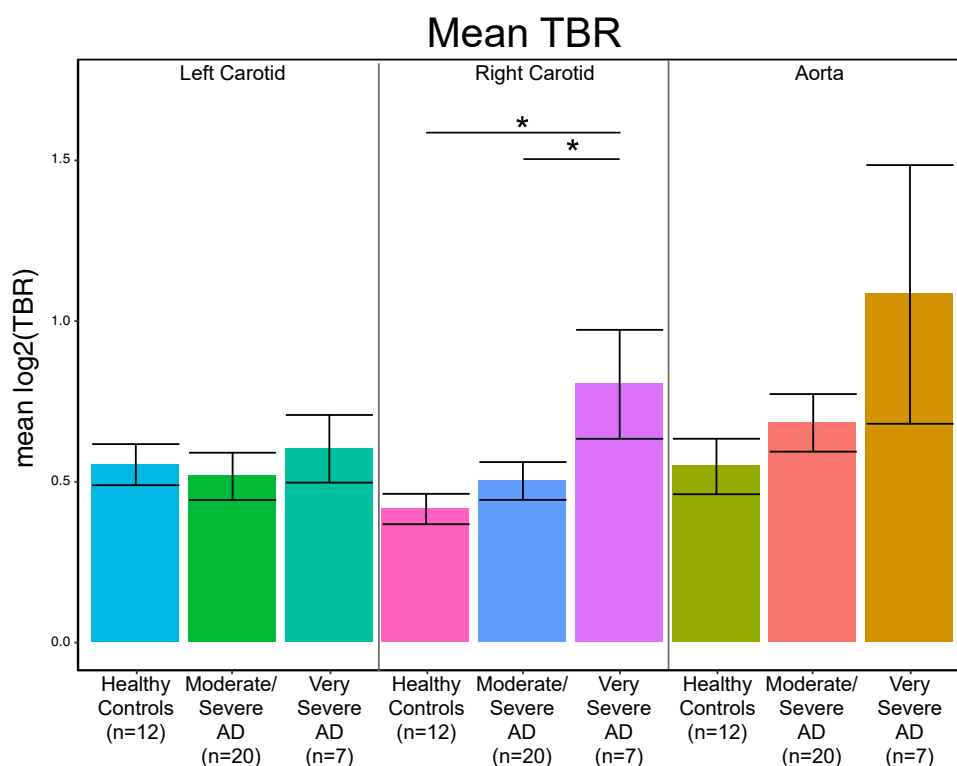
[†]P < .05.[‡]P < .1.

FIGURE 3. Mean target-to-background ratio (TBR) in health controls, patients with moderate and severe atopic dermatitis (AD), and patients with very severe AD. Mean TBR in the carotid arteries and aortas of healthy controls, patients with moderate and severe AD, and patients with very severe AD. *P < .05.

(log₂FCH = 0.68, FCH = 1.60, P = .04) and by MDS TBR (log₂FCH = 0.79, FCH = 1.73, P = .03). FCHs and P values for all comparisons are listed in Table II.

DISCUSSION

Inflammatory diseases such as rheumatoid arthritis,²³ and more recently, psoriasis,^{12,16,24} have been associated with systemic

inflammation, as well as with increased risk of cardiovascular disease. These diseases were also associated with increased vascular inflammation as assessed by different imaging modalities, including ¹⁸F-FDG-PET/CT^{16,18,25,26} and CT angiography.^{12,15} Furthermore, these imaging techniques were further applied to show that vascular inflammation can be reversed with new anti-inflammatory treatments.¹⁶

In AD, there are emerging epidemiological data of increased cardiovascular comorbidities, including hypertension and heart disease in certain populations.⁵⁻¹⁰ These epidemiological data are also supported by increases in circulation of moderate-to-severe AD patients of inflammatory proteins, including cardiovascular/atherosclerosis markers, compared to controls, and even to moderate-to-severe psoriasis patients. The increases in systemic immune and cardiovascular markers in patients with moderate-to-severe AD have been recently suggested to potentially originate and correlate with levels in lesional skin.²⁷ Consistent with this, coronary calcification has been shown in patients with severe AD without established cardiac disease. Nevertheless, imaging with ¹⁸F-FDG-PET/MRI to identify increased cardiovascular inflammation, which is a surrogate for active atherosclerotic disease,¹³ has not been used in AD. In view of rapid development of therapeutics in AD, its application to AD can potentially serve as a valuable tool to assess reversibility of vascular inflammation with various treatments.

It is currently thought that chronic inflammation may accelerate atherosclerosis, potentially due to repetitive vascular injury.²⁸ In psoriasis, cutaneous and systemic inflammation is centered on elevated levels of IL-17, IL-22, and TNF- α , and these cytokines are currently believed to contribute to the increased cardiovascular risk in psoriasis.^{24,29} In AD skin, there is significant upregulation of IL-13 and IL-22 cytokines.^{30,31} Increased systemic immune activation has also been observed in blood of patients with moderate-to-severe AD,^{27,32,33} with increases in both skin homing and systemic T-cell subsets when compared with healthy controls.³⁴ IL-13 has also been shown to be elevated in blood from patients with AD.^{33,35} Of note, AD is associated with even higher activation of skin homing T-cell subsets when compared with psoriasis.³⁶ These observations point to an increased burden of not only skin, but also systemic inflammation in patients with moderate-to-severe AD.

CRP, an acute phase reactant, is a widely accepted biomarker for atherosclerotic disease, with prognostic value in predicting cardiovascular events.³⁷ In psoriasis, CRP is significantly elevated and associated with skin disease severity.³⁸ Importantly, CRP serum levels were identified as significantly increased in patients with moderate-to-severe AD when compared with matched healthy controls.²¹ Furthermore, a robust signature in blood from patients with moderate-to-severe AD (defined through high-throughput proteomic assays) highlighted significant dysregulation of inflammatory and cardiovascular risk markers,³⁵ perhaps originating from the robust skin inflammation.^{27,33,35,39,40} The increases in skin and serum inflammatory and cardiovascular risk factors, together with hyperactivated circulating T cells and increased coronary artery calcifications, strongly support the systemic nature of AD extending beyond classic atopic/allergic associations.

This preliminary study is the first to establish a trend for greater vascular inflammation in patients with moderate-to-severe AD, as seen in the aortas and right carotid arteries versus healthy controls in this study cohort. Based on the measurements of mean TBR, a conservative estimate of total vessel inflammation, max TBR, and MDS TBR, an estimate of the greatest focal inflammation in the vessel, different levels of statistical significance were observed; however, regardless of the specific TBR measure used, there was a clear trend toward greater inflammation in the AD group versus controls. In addition, clinical severity of patients with AD measured by EASI correlated

with both the CRP level and the extent of inflammation within their right carotid arteries. Furthermore, stratifying patients with AD by clinical severity into patients with moderate/severe and very severe AD revealed higher TBRs for very severe AD than both moderate/severe patients and healthy controls. In contrast, patients with moderate/severe AD did not have elevated TBRs versus controls. Taken together, these observations suggest that there may be a relationship between the level of systemic inflammation in patients with AD and their level of vascular inflammation. Of note, no differences in TBRs were identified in the left carotid arteries between patients with AD and healthy controls. The asymmetric distribution of vascular injury might be rooted in the different anatomy between the right and the left carotid arteries (arising from the brachiocephalic trunk versus from the aortic arch, respectively), which influences local hemodynamic forces.⁴¹

Differential carotid intima media thickness has also been observed in multiple other studies,⁴²⁻⁴⁴ typically with greater thickening of the left carotid vessels. The differential results between the carotids observed in this study will require investigation in future studies larger cohorts.

We must acknowledge several limitations. The sample size was small (particularly for healthy controls); thus it is likely that the study was underpowered to detect differences with higher levels of confidence. In addition, only 4 patients with moderate AD were included, preventing further stratification and analysis separating moderate from severe and very severe patients. Lastly, total cholesterol levels were significantly elevated among patients with AD compared with healthy controls. As cholesterol levels are known to contribute to vascular inflammation, this may represent a confounding factor. When comparing a subset of patients with AD with matched total cholesterol levels with healthy controls, there was a trend to significant elevation of vascular inflammation that supports the validity of our findings; however, this comparison was limited by a small sample size. Future studies with much larger patient cohorts are needed to elucidate the relationship between chronic systemic inflammation in AD, cardiovascular inflammation as a surrogate for atherosclerotic disease, and ultimately, risk for cardiovascular events. Furthermore, evaluation of vessel inflammation before and after treatment, as has been done in psoriasis,^{16,45} showing decreased inflammation after treatment, will help to determine the extent to which vascular inflammation in AD is modifiable.

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