ORIGINAL REPORT

Therapeutic Effect of Dupilumab on Systemic and Vascular Inflammation in Adults with Severe Atopic Dermatitis: Feasibility Study Using 18F-Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography

Gi-Wook LEE[1#], Keunyoung KIM[2,3#], Seong-Jang KIM[2], Kihyuk SHIN[1], Hoonsoo KIM[1,3], Hyun-Chang KO[1], Moon-Bum KIM[1,3] and Byungsoo KIM[1,3]

[1]Department of Dermatology, School of Medicine, Pusan National University, Busan, Korea, [2]Department of Nuclear Medicine, and [3]Biomedical Research Institute, Pusan National University Hospital, Busan, Korea
[#]These authors contributed equally to this study and should be considered as co-first authors.

Atopic dermatitis (AD) is an inflammatory skin disease associated with increased systemic and vascular inflammation. Although dupilumab has been proven to be effective against severe AD, imaging studies analysing its inflammation-reducing effect have rarely been reported. The aim of this study was to evaluate the effect of dupilumab on systemic and vascular inflammation in adult patients with severe AD, using 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT). A total of 33 adult patients with severe AD and 25 healthy controls underwent 18F-FDG PET/CT at baseline. Patients on dupilumab treatment underwent 18F-FDG PET/CT again after achieving a 75% reduction from baseline on the Eczema Area and Severity Index (EASI-75). Patients with AD exhibited increased 18F-FDG uptake values in the liver, spleen, pancreas, and carotid artery compared with healthy controls. However, compared with baseline, there was no statistically significant difference in 18F-FDG uptake in major organs and arteries after achieving EASI-75 with dupilumab treatment. In conclusion, while dupilumab treatment resulted in a significant clinical improvement and reduced serum inflammatory markers in adult patients with severe AD, no changes in systemic and vascular inflammation were observed on 18F-FDG PET/CT imaging.

Key words: atopic dermatitis; cardiovascular disease; comorbidity; dupilumab; inflammation; PET/CT: positron emission tomography-computed tomography.

Corr: Byungsoo Kim, Department of Dermatology, School of Medicine, Pusan National University, 179 Gudeok-ro, Seo-gu 49241, Busan, Korea. E-mail: dockbs@pusan.ac.kr

SIGNIFICANCE

Dupilumab is an effective treatment for atopic dermatitis; however, data on its systemic effects are limited. Patients with atopic dermatitis have increased vascular inflammation according to clinical severity. However, this study found that the changes in systemic and vascular inflammation after dupilumab treatment were not significant. Special attention is required to determine whether atopic dermatitis treatment not only improves skin symptoms, but also improves systemic and vascular inflammation.

Atopic dermatitis (AD) is a common chronic inflammatory disease that is associated with numerous comorbidities, including cardiovascular and systemic diseases (1–3). Notably, analysis of the 2002–2012 Nationwide Inpatient Sample of adults in the USA found that AD was associated with increased odds (odds ratio [95% confidence interval] 1.18 [1.14–1.22]) of vascular, cardiovascular, and cerebrovascular diseases (4). Recent data have explained this association using the concept of inflammatory skin march, which occurs when a vast range of proinflammatory cytokines and chemokines from the lesional skin enter the circulatory system and cause systemic inflammation and other comorbidities (3). Although standard systemic inflammation markers, such as high-sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR) can reflect systemic inflammation in AD, novel assessment modalities providing regional inflammation *in vivo* are still required to understand the association between AD, systemic inflammation and comorbidities. 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) is a validated functional imaging modality for the diagnosis and management of malignancies, which can also be used to successfully evaluate benign inflammatory diseases with high sensitivity (5, 6). Because enhanced glycolytic activity is a hallmark of activated inflammatory cells, combined PET and CT imaging provides visualization of accumulation of acute and chronic inflammatory cells resulting from primary atherosclerosis or secondary to systemic inflammatory diseases (7, 8). Thus, 18F-FDG PET/CT is used as a measurement tool to evaluate inflammatory activity, including vascular, visceral, and whole-body inflammation *in vivo* (6). These trials have been attempted in several previous studies in the field of psoriasis (8–10). 18F-FDG PET/CT was used to evaluate systemic and vascular inflammation in patients with psoriasis; in addition, an improvement in inflammation after treatment was also

confirmed by ^{18}F-FDG PET/CT. Although increased vascular inflammation in AD was confirmed in a recent study using PET/magnetic resonance imaging (MRI), the data are still limited (11). Furthermore, the improvement in inflammation after treatment has not yet been evaluated. The aim of the current study was therefore to assess systemic and vascular inflammation using ^{18}F-FDG PET/CT in patients with severe AD and to evaluate whether dupilumab, an interleukin (IL)-4 receptor α-antagonist that modulates the signalling of IL-4 and IL-13 pathways, could have a positive effect on reducing inflammation in these patients.

MATERIALS AND METHODS

Study population

This study included patients aged 18–70 years who were diagnosed with AD according to the Hanifin and Rajka diagnostic criteria and had had AD for over 3 years (12). Diagnostic confirmation and severity assessment were performed by 2 experienced dermatologists. Patients were eligible if they were candidates for dupilumab therapy with Eczema Area and Severity Index (EASI) >23, who did not respond to topical therapy or oral cyclosporine or methotrexate therapy for at least 3 months (13). The exclusion criteria included factors that could increase systemic or vascular inflammation, such as a history of malignant tumours within the past 5 years, uncontrolled diabetes mellitus and hypertension, uncontrolled dyslipidaemia, major surgery within 3 months, and active infection within the preceding 72 h. Twenty-five healthy controls without any history of systemic and/or cutaneous inflammatory disease underwent the same protocol at baseline. The study protocol was approved by the Pusan National University Hospital Institutional Review Board and all patients provided informed consent (IRB number 2001-022-087).

Study design

After initial screening, 33 patients with AD and 25 healthy controls underwent ^{18}F-FDG PET/CT imaging and laboratory testing (complete blood count, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), ESR, and CRP). Of the 33 patients with AD included in this study, 25 patients treated with dupilumab underwent ^{18}F-FDG PET/CT and laboratory testing again after achieving a 75% reduction from baseline on EASI (EASI-75). The levels of inflammation in large organs, including the liver, spleen, and pancreas, and major arteries, including the carotid artery, thoracic aorta, and abdominal aorta, in patients with AD were compared with those in healthy controls. Moreover, the current study determined the relationship between the severity of inflammation with sex, obesity, and clinical severity of AD in the AD group. Finally, the study evaluated the changes in arterial and visceral inflammation after EASI-75 was achieved with dupilumab.

Imaging studies

PET/CT protocol. All patients fasted and rested for at least 6 h before undergoing ^{18}F-FDG PET/CT imaging, since serum glucose levels needed to be below 120 mg/dL before ^{18}F-FDG administration. A dose of 370 MBq (10 mCi) ^{18}F-FDG was injected intravenously 60 min prior to PET/CT scanning. The patients were scanned from vertex to toe using a Gemini TF ^{18}F-FDG PET/CT scanner (Gemini TF, Philips, Milpitas, CA, USA). The emission

scan time per bed position was 3 min, and 6 bed positions were used. PET data were obtained using a high-resolution whole-body scanner with an axial field of view of 21.6 cm. The mean axial resolution varied between 2 mm full width at half maximum at the centre and 2.4 mm at 28 cm. The mean total PET/CT examination time was 20 min. Attenuation correction was performed in all patients with iterative reconstruction. PET/CT images were analysed in 3 different planes: transverse, coronal, and sagittal.

Standard uptake values measurement.

The ^{18}F-FDG PET/CT datasets were reviewed retrospectively by 2 experienced nuclear medicine specialists. ^{18}F-FDG uptake was quantified by drawing a region of interest around the liver, spleen, pancreas, and each part of the artery on every slice of the co-registered ^{18}F-FDG PET/CT image. To evaluate systemic inflammation, the maximum standard uptake values (SUV) of the liver, spleen, pancreas, and vascular inflammation, and those in the carotid artery, thoracic aorta, and abdominal aorta were examined by the circular region of interest (ROI) placed on the axial plane, where the most intense uptake was visualized for each organ. Using the CT images for co-registration, the areas of interest were identified on the PET images.

Statistical analysis

The AD and healthy groups were compared using 2-sided *t*-tests for normally distributed continuous variables and the Mann–Whitney *U* tests for non-parametric variables. To assess the changes within each group, a paired *t*-test was performed. Two-tailed probability values were reported, and statistical significance was assumed when the *p*-value was <0.05. Descriptive data were presented as the mean ± standard deviation (SD) for continuous parametric variables.

Table I. Clinical characteristics of study participants

Characteristics	AD (n = 33)	Healthy (n = 25)	p-value
Age, years, mean ± SD	30.73 ± 9.77	39.6 ± 1.58	0.000
Sex, n (%)			0.052
Male	25 (75.8)	12 (48)	
Female	8 (24.2)	13 (52)	
Previous treatments, n (%)			
Topical calcineurin inhibitors	33 (100)		
Topical corticosteroids	32 (96.9)		
Oral cyclosporine	31 (93.9)		
Oral methotrexate	9 (27.3)		
EASI, mean ± SD	31.71 ± 8.74		NA
Body mass index, kg/m², mean ± SD	24.42 ± 3.45	23.04 ± 3.22	0.179
Total cholesterol, mg/dL, mean ± SD	170.54 ± 38.98	200.63 ± 34.64	0.003
LDL cholesterol, mg/dL, mean ± SD	92.8 ± 35.45	123.38 ± 40.18	0.005
Triglycerides, mg/dL, mean ± SD	136.97 ± 66.84	130.13 ± 91.83	0.396
HDL cholesterol, mg/dL, mean ± SD	50.35 ± 9.99	60.83 ± 14.32	0.008
ESR, mg/dL, mean ± SD	16.30 ± 9.4	NA	NA
CRP, mg/dL, mean ± SD	0.29 ± 0.41	0.01 ± 0.03	0.000
Leucocytes, 10³/L, mean ± SD	8.74 ± 2.66	5.71 ± 1.08	0.000
Neutrophils, 10³/L, mean ± SD	59.51 ± 11.27	11.27 ± 7.18	0.193
Lymphocytes, %, mean ± SD	21.37 ± 7.76	7.76 ± 5.81	0.000
Monocytes, %, mean ± SD	7.23 ± 2.22	2.23 ± 1.26	0.101
Baseline PET/CT values, mean ± SD			
Liver	1.37 ± 0.22	1.2 ± 0.19	0.016
Spleen	1.1 ± 0.16	0.97 ± 0.1	0.003
Pancreas	0.94 ± 0.18	0.73 ± 0.1	0.000
Carotid artery	0.95 ± 0.36	0.78 ± 0.06	0.011
Thoracic aorta	1.12 ± 0.24	1.02 ± 0.09	0.097
Abdominal aorta	1.12 ± 0.37	1.05 ± 0.13	0.351

AD: atopic dermatitis; SD: standard deviation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NA: not applicable; EASI: Eczema Area and Severity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PET/CT: positron emission tomography-computed tomography.
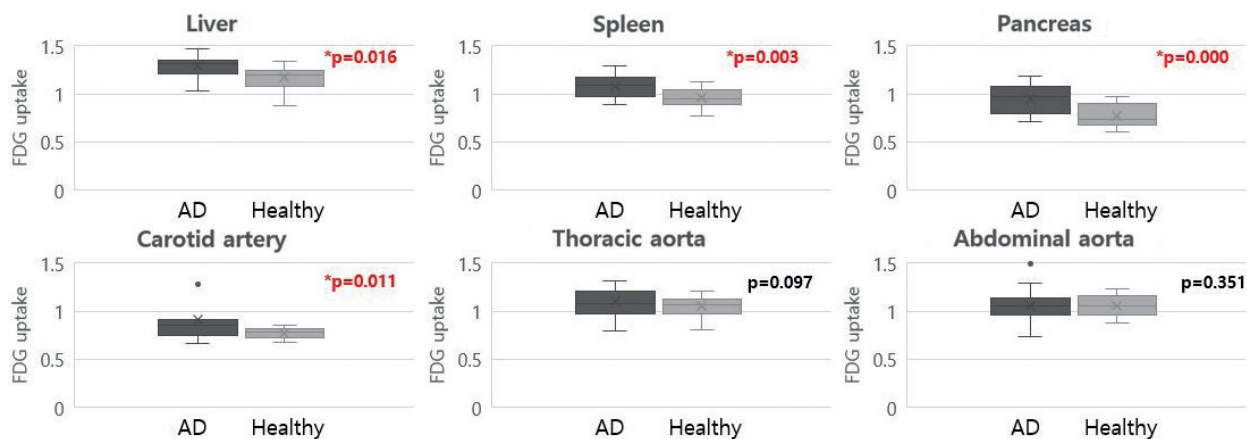
Fig. 1. Comparison of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake between atopic dermatitis (AD) (*n* = 33) and healthy controls (*n* = 25) using positron emission tomography-computed tomography (PET/CT) imaging. The y-axis represents the standard uptake value of ¹⁸F-FDG. Bars indicate the mean ± standard deviation values. *Statistically significant (*p* < 0.05).

RESULTS

Patients' characteristics

The demographics and clinical characteristics of the study participants are shown in **Table I**. The basic demographic profiles did not differ significantly between the patients with AD and healthy controls, except for higher age in the healthy control group. Patients with AD were observed to have a mean EASI of 31.7. Among the patients with AD, 33 were treated with topical calcineurin inhibitors, 32 with topical corticosteroids, 31 with cyclosporine, and 9 with methotrexate.

Comparisons of ¹⁸F-fluorodeoxyglucose uptake between atopic dermatitis and healthy control groups

Baseline ¹⁸F-FDG PET/CT imaging revealed greater increases in the ¹⁸F-FDG uptake in the liver, spleen,
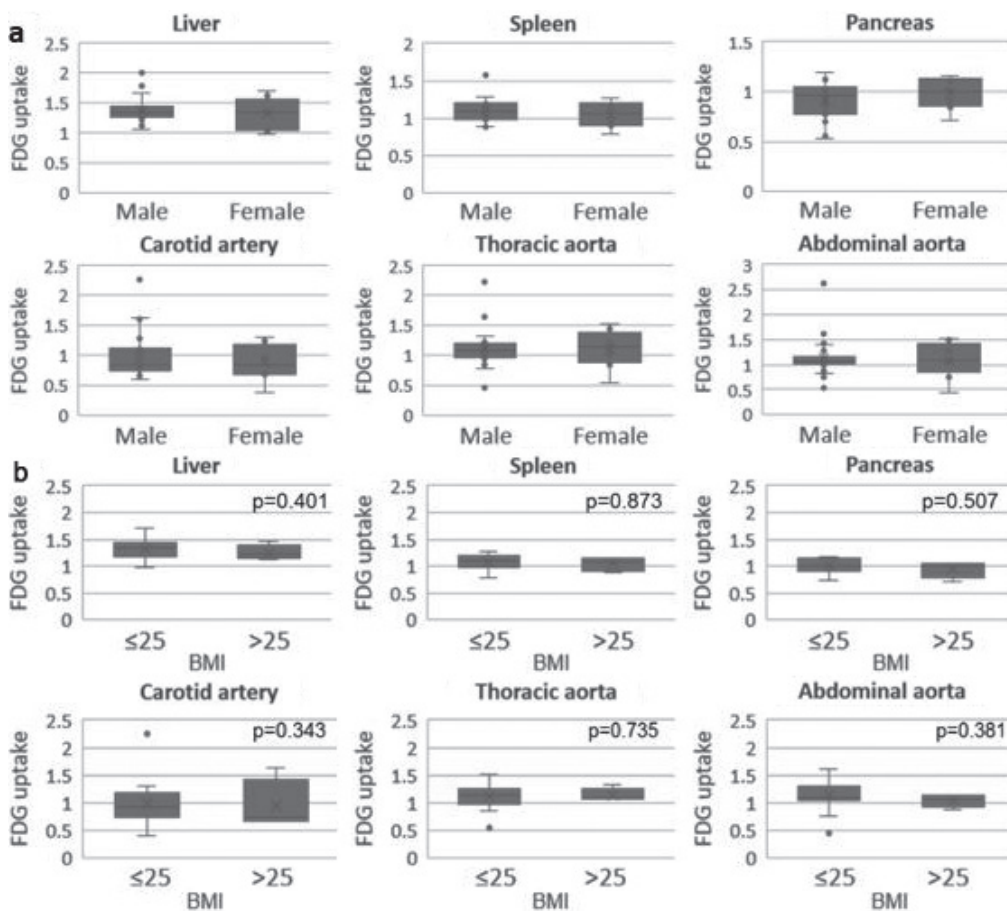
Fig. 2. Comparison of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake in positron emission tomography-computed tomography (PET/CT) imaging by (a) sex and (b) body mass index (BMI) among patients with atopic dermatitis (AD). ¹⁸F-FDG uptake level showed no significant difference in the major organs and all parts of the arteries according to sex and BMI. *Statistically significant (*p* < 0.05).
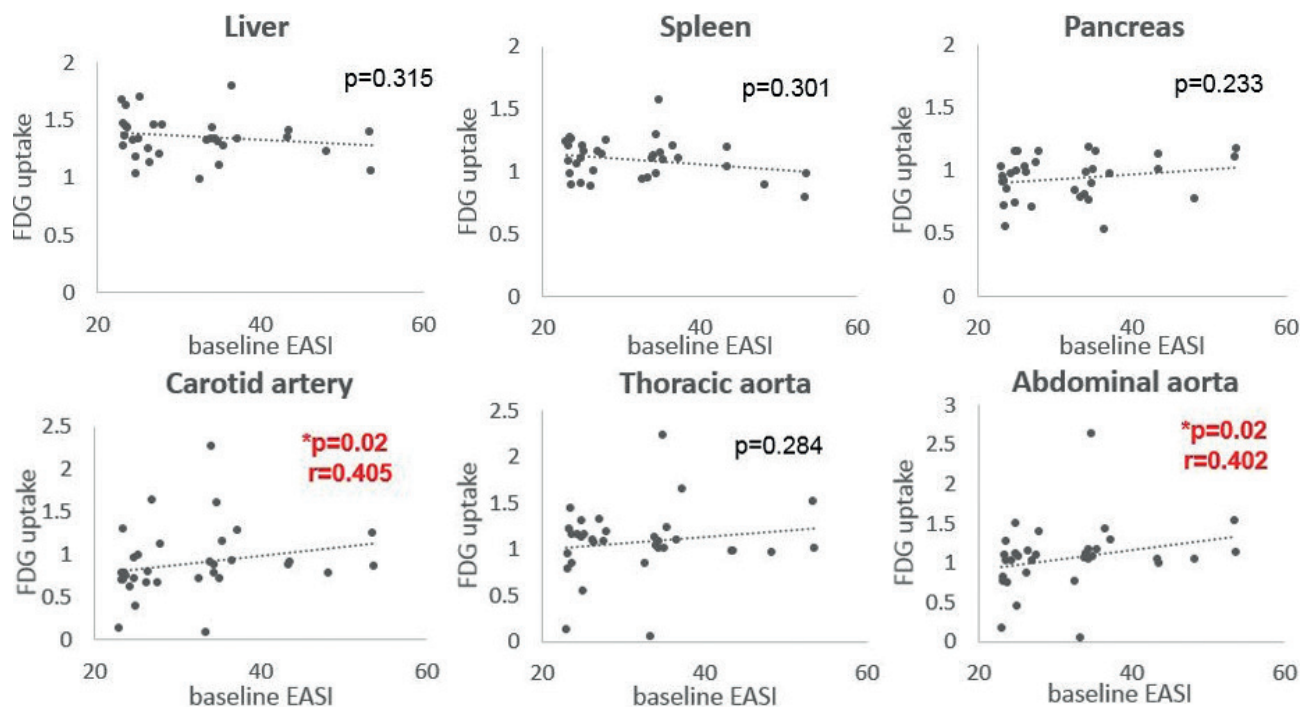
Fig. 3. Correlation between the baseline Eczema Area and Severity Index (EASI) and ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake in positron emission tomography-computed tomography (PET/CT) imaging in patients with atopic dermatitis (AD). Baseline EASI score correlates with ¹⁸F-FDG uptake in the carotid artery and abdominal aorta.

pancreas, and carotid artery in the AD group than in healthy controls. There was no significant difference in the thoracic and abdominal aorta between the patients with AD and healthy controls (**Fig. 1**).

Comparisons of ¹⁸F-fluorodeoxyglucose uptake among patients with atopic dermatitis

Among the patients with AD, there was no significant difference in the ¹⁸F-FDG uptake in the major organs and

all parts of the aorta, according to sex and body mass index (BMI) at baseline (**Fig. 2**). However, a positive correlation was found between the baseline EASI score and ¹⁸F-FDG uptake in the carotid artery and abdominal aorta (*p* < 0.05) (**Fig. 3**).

Comparisons of ¹⁸F-fluorodeoxyglucose uptake before and after dupilumab treatment

After EASI-75 was achieved with dupilumab treatment for a mean period of 18.9 weeks, the mean EASI score was reduced from 31.7 to 5.75; an improvement of 81.9%. The levels of inflammatory markers (ESR and hsCRP) also decreased significantly after dupilumab treatment (**Table II**). However, there was no significant difference in ¹⁸F-FDG uptake in major organs and all parts of the aorta after dupilumab treatment (**Fig. 4**).

DISCUSSION

Through its association with various systemic comorbidities, several studies have been conducted to prove that AD is a systemic disease (14, 15). Beyond molecular analysis, the current study focused on assessing the increase in systemic and vascular inflammation in patients with AD through imaging modalities. The study also evaluated whether systemic and vascular inflammation were modifiable through treatment.

The results showed that patients with AD had increased inflammation in the liver, spleen, pancreas, and carotid

Table II. Comparison of characteristics before and after dupilumab treatment in patients with atopic dermatitis (AD)

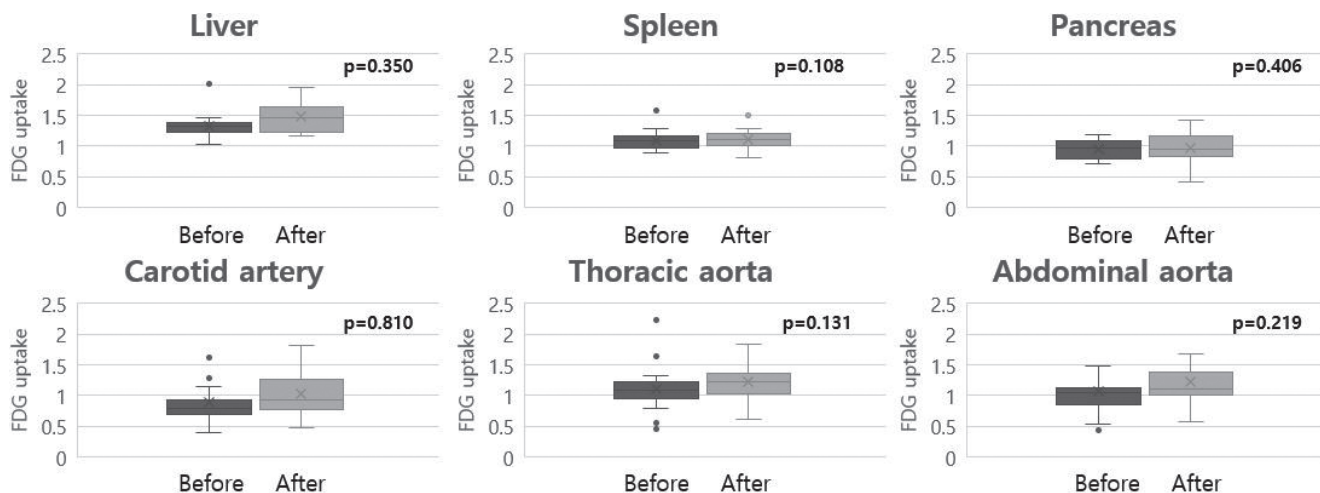| Characteristics	Baseline (n = 25)	After dupilumab (n = 25)	p-value
Age, years, mean ± SD	29.92 ± 8.90		
Sex, n (%)			
Male	22 (88.0)		
Female	3 (12.0)		
Previous treatments, n (%)			
Topical calcineurin inhibitors	25 (100)		
Topical corticosteroids	24 (96.0)		
Oral cyclosporine	25 (100)		
Oral methotrexate	7 (28.0)		
EASI, mean ± SD	31.64 ± 8.58	5.75 ± 2.52	0.000
Body mass index, kg/m², mean ± SD	24.98 ± 3.56	23.04 ± 3.22	0.179
ESR, mg/dL, mean ± SD	16.05 ± 9.90	8.26 ± 5.44	0.014
CRP, mg/dL, mean ± SD	0.34 ± 0.46	0.08 ± 0.08	0.041
Leucocytes, 10³/L, mean ± SD	8.56 ± 2.19	7.90 ± 1.84	0.000
Neutrophils, 10³/L, mean ± SD	59.06 ± 11.04	52.78 ± 14.15	0.193
Lymphocytes, %, mean ± SD	22.21 ± 7.77	26.79 ± 7.54	0.000
Monocytes, %, mean ± SD	7.45 ± 2.2	7.93 ± 1.85	0.101

SD: standard deviation; EASI: Eczema Area and Severity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Fig. 4. Comparison of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake in positron emission tomography-computed tomography (PET/CT) imaging before and after dupilumab treatment. No significant differences in ¹⁸F-FDG uptake in major organs and all parts of the arteries after dupilumab treatment.

artery compared with healthy controls. It is known that future cardiovascular disease (CVD) events can be predicted from increased ¹⁸F-FDG uptake of the arteries; thus, the current findings imply that adult patients with severe AD have a higher CVD risk than healthy individuals (9, 11, 16). Furthermore, the current study showed a positive correlation between baseline EASI scores and ¹⁸F-FDG uptake in the carotid artery and abdominal aorta, which suggests that severe skin inflammation may accompany vascular inflammation in AD. This result is in accordance with a previous report that showed higher vascular inflammatory activity for severe AD than for moderate AD and healthy control groups using ¹⁸F-FDG PET/MRI (11). However, there was no significant association between ¹⁸F-FDG uptake and sex and BMI. It is assumed that the relatively young age of the study participants and their demographic characteristics with less metabolic syndrome may have influenced these results.

The current study also analysed whether a significant reduction in AD severity with dupilumab treatment could modulate these values. A total of 18.9 weeks of dupilumab therapy (mean 10 injections) decreased the clinical severity of AD by a mean of 81.9%. In addition to clinical improvement, there was a significant decrease in ESR and hsCRP levels after dupilumab treatment. However, no significant changes in systemic or vascular inflammation were detected on ¹⁸F-FDG PET/CT imaging. Thus, it was assumed that the following factors could contributed to the discrepancies between the result of this study with those of our previous study on psoriasis (10). Firstly, dupilumab treatment may be less effective in reducing vascular inflammation because the Th2 pathway is still controversial in the pathogenesis of atherosclerosis; in addition, evidence on whether reducing vascular inflammation could lower the risk of CVD is lacking (17–19). Although Villani et al. (15) showed dysregulation of atherosclerosis-related genes after dupilumab treatments

in patients with AD, they did not reveal an improvement in vascular inflammation after treatment with ¹⁸F-FDG PET/CT. Secondly, an overall lower uptake of ¹⁸F-FDG by major organs and vessels in patients with AD compared with in patients with psoriasis may have influenced the results. These differences can be explained by the fact that patients with AD are relatively young and have fewer comorbidities (e.g. hyperlipidaemia, obesity, diabetes, and ischaemic heart disease) (20).

Numerous studies suggest that serum markers, such as ESR, hsCRP, and leukocyte count, could be independent predictors of future cardiovascular events in both healthy individuals and in patients with several CVDs (21, 22). In the current study, baseline serum hsCRP levels in the AD group were significantly higher than those in the healthy control group. In addition, this level decreased after treatment with dupilumab. These changes in inflammatory serum markers suggest that dupilumab may be effective in preventing cardiovascular complications in patients with severe adult AD.

However, PET/CT did not show the same results as serum inflammatory markers for dupilumab treatment, which may be evaluated as showing limitations in PET/CT sensitivity. The current study has some limitations. First, the study did not compare patients with AD with age- and sex-matched healthy controls, which might have influenced the differences in ¹⁸F-FDG uptake in major organs between patients with AD and healthy controls. Secondly, previous use of cyclosporine or methotrexate might have influenced the results of ¹⁸F-FDG uptake. The difference according to the duration of drug use was not reflected in the study. Thirdly, the small sample size may have decreased the statistical power of the current results. Fourthly, assessment of atopic comorbidities, such as asthma or allergic rhinitis, was not considered. As these diseases often coexist with AD and are associated with Th2-driven inflammation, this may have influenced the

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outcome. Finally, since the current study did not report on systemic or cardiovascular events in patients in the long-term follow-up, it is not clear whether the increase in inflammation detected through imaging modalities has a meaningful clinical effect. In conclusion, special attention is required to determine whether AD treatment not only improves skin symptoms, but also improves systemic and vascular inflammation.

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The authors have no conflicts of interest to declare.

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