Ustekinumab treatment is associated with decreased systemic and vascular inflammation in patients with moderate-to-severe psoriasis: Feasibility study using ^{18}F-fluorodeoxyglucose PET/CT

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Background: Evidence suggests that psoriasis might be associated with metabolic syndrome and an increased risk for cardiovascular disease.

Objective: To determine whether ustekinumab reduces systemic and vascular inflammation associated with metabolic syndrome and cardiovascular disease, measured using ^{18}F-fluorodeoxyglucose positron emission tomography—computed tomography (^{18}F-FDG PET/CT).

Methods: Patients with psoriasis and healthy controls underwent baseline ^{18}F-FDG PET/CT imaging. Patients with moderate-to-severe psoriasis were treated with ustekinumab and underwent ^{18}F-FDG PET/CT again after a Psoriasis Area and Severity Index of 75 was achieved.

Results: After a Psoriasis Area and Severity Index of 75 was achieved with ustekinumab treatment, standardized uptake values were reduced in the liver, spleen, and 5 parts of the aorta ($P < .05$).

Limitations: Our study does not provide outcome data concerning cardiovascular events or metabolic syndrome; it only shows surrogate markers in a limited (Korean) population.

Conclusion: Ustekinumab treatment was significantly associated with decreased systemic and vascular inflammation related to metabolic syndrome and cardiovascular disease among patients with psoriasis. (J Am Acad Dermatol 2019;80:1322-31.)

Key words: cardiovascular disease; metabolic syndrome; PET/CT; positron emission tomography—computed tomography; psoriasis; ustekinumab.

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Psoriasis, a systemic inflammatory disease, is reportedly associated with a high prevalence of metabolic syndrome, including central obesity, dyslipidemia, glucose intolerance, and elevated blood pressure. Furthermore, several reports suggest that psoriasis is an independent risk factor for cardiovascular and cerebrovascular diseases.[1-4] However, despite evidence of systemic inflammation in psoriasis, the location of inflammation in vivo is difficult to identify and quantify in these patients. Standard systemic inflammation markers, such as high-sensitivity C-reactive protein and erythrocyte sedimentation rate, only modestly correlate with psoriasis severity and do not provide regional information about disease involvement. Therefore, novel assessments of inflammation in vivo are particularly important to understand the impact of psoriasis on systemic inflammation and systemic comorbidities.[5]

CAPSULE SUMMARY

- Psoriasis might be associated with metabolic syndrome and an increased risk for cardiovascular disease.
- Patients with psoriasis had increased hepatic, splenic, and arterial inflammation that decreased with ustekinumab therapy.
- Ustekinumab treatment was significantly associated with decreased systemic and vascular inflammation related to metabolic syndrome and cardiovascular disease among patients with psoriasis.

The usefulness of ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography (^{18}F-FDG PET/CT) for measuring arterial, visceral, and whole-body inflammation in vivo has been investigated.[6] Arterial ^{18}F-FDG uptake correlates with the burden of cardiovascular risk factors,[7-10] is elevated after recent atherothrombotic events,[11,12] and could predict future atherothrombotic risk.[13,14] Two recent reports evaluated visceral and arterial inflammation in patients with psoriasis by using ^{18}F-FDG PET/CT.[15,16] In these pilot studies, ^{18}F-FDG PET/CT readily identified visceral inflammation, including hepatic and psoriatic lesional skin inflammation. These results suggest that tissue inflammation in patients with psoriasis could be assessed by using ^{18}F-FDG PET/CT.

Although ustekinumab, an anti-interleukin 12/23 IgG1κ human monoclonal antibody, has proven to be effective for treating cutaneous psoriasis, there is uncertainty whether it can produce remission in psoriatic comorbidities, especially in cases of systemic and vascular inflammation.

In this study, we investigated inflammation in 25 patients with psoriasis to determine the differences in the subclinical inflammation of the major arteries and large viscera, including the liver and spleen, compared with that of age-matched, sex-matched healthy subjects. The second part of the study aimed to determine the relationship of inflammation severity to psoriasis severity, obesity, and age in the psoriasis group. Finally, we evaluated the changes in arterial and visceral inflammation after a 75% improvement from baseline in the Psoriasis Area and Severity Index (PASI75) was achieved with ustekinumab.

METHODS

Study populations

^{18}F-FDG PET/CT was performed in a consecutive sample of patients (n = 25) aged 18-70 years who were given the diagnosed of psoriasis vulgaris at least 6 months earlier. The patients who were eligible for ustekinumab therapy were 18-70 years of age, had chronic moderate-to-severe plaque psoriasis, were candidates for phototherapy or systemic treatment, had a PASI of >10, and had at least 10% of the body surface area (BSA) affected at baseline. Diagnostic confirmation of plaque psoriasis and assessment of BSA and PASI were performed by 2 experienced dermatology specialists.

Patients were ineligible for participation in the study if they had nonplaque (ie, pustular, guttate, or erythrodermic) or drug-induced forms of psoriasis. The exclusion criteria also included factors that can increase systemic or vascular inflammation, such as

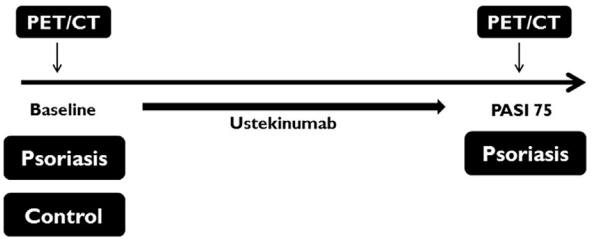

Fig 1. Study design. Patients with psoriasis and age-matched, sex-matched healthy controls underwent baseline ^{18}F-FDG PET/CT imaging. Among patients with psoriasis, patients with moderate-to-severe psoriasis were treated with ustekinumab, and ^{18}F-FDG PET/CT images were obtained again after PASI75 was achieved following ustekinumab initiation. *^{18}F-FDG PET/CT*, ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography; *PASI75*, 75% improvement from baseline Psoriasis Area and Severity Index score; *PET/CT*, positron emission tomography–computed tomography.

Abbreviations used:

BMI:	body mass index
BSA:	body surface area
CVD:	cardiovascular disease
PASI:	Psoriasis Area and Severity Index
PASI75:	75% improvement from baseline Psoriasis Area and Severity Index score
^{18}F-FDG PET/CT:	^{18}F-fluorodeoxyglucose positron emission tomography—computed tomography

tobacco use, regular use of alcoholic beverages (2 drinks/day), hypertension, dyslipidemia, diabetes mellitus, history of cerebrovascular disease, warfarin sodium use, coagulopathy, pregnancy or lactation, nondermatologic malignant disease within the past 5 years, positive human immunodeficiency virus status, major surgery within the past 3 months, and history of intravenous drug use or active infection within the preceding 72 hours. The study was approved by the hospital ethics committee, and all the patients provided informed consent (IRB 1203-001-003).

Study design

After initial screening, 25 patients with psoriasis and 47 age-matched, sex-matched healthy controls underwent baseline ^{18}F-FDG PET/CT imaging. Among the patients with psoriasis, 10 who had moderate-to-severe psoriasis treated with ustekinumab underwent ^{18}F-FDG PET/CT again after PASI75 was achieved (Fig 1).

^{18}F-FDG PET/CT imaging

All ^{18}F-FDG PET/CT scans were obtained at the department of nuclear medicine. After a ≥6-hour fast to achieve a blood glucose level of <140 mg/kg, 5.18-MBq/kg ^{18}F-fluorodeoxyglucose (^{18}F-FDG) was given intravenously. After a 1-hour rest, the patients were scanned from the skull base to the proximal thigh by using a Gemini TF ^{18}F-FDG PET/CT scanner (Gemini TF, Philips, Milpitas, CA).

The ^{18}F-FDG PET/CT data sets were reviewed retrospectively by 2 experienced nuclear medicine specialists. Systemic inflammation was measured in the liver and spleen, and vascular inflammation was measured in 5 parts of the

Table I. Clinical characteristics of study participants

Characteristic	Psoriasis, n = 25	Healthy controls, n = 47	*P* value
Age, years	44.2 ± 9.1	47.5 ± 7.2	.0977
Sex, male, % (n)	68 (17)	60 (28)	.655
Body mass index, kg/m^2	24.8 ± 4.7	23.8 ± 3.2	.2121
% Body surface area involved	32.9 ± 20.6	NA	NA
PASI	13.1 ± 8.7	NA	NA
Total cholesterol, mg/dL	199.38 ± 43.57	187.79 ± 27.80	.5908
LDL cholesterol, mg/dL	120.88 ± 39.09	118.23 ± 25.30	.7960
Triglycerides, mg/dL	162.41 ± 88.98	144.28 ± 86.04	.8137
HDL cholesterol, mg/dL	52.18 ± 11.56	50.49 ± 12.92	.6925
C-reactive protein, mg/dL	0.28 ± 0.34	0.07 ± 0.08	.0050
Leucocytes, $10^3/\mu$L	7.70 ± 2.24	5.89 ± 1.63	.0001
Neutrophils, $10^3/\mu$L	60.11 ± 9.59	54.50 ± 9.23	.0156
Lymphocytes, %	29.28 ± 8.35	35.00 ± 8.08	.0107
Monocytes, %	12.68 ± 27.28	6.97 ± 1.86	.4844
Baseline PET/CT values			
Liver	2.00 ± 0.29	2.45 ± 0.56	.001
Spleen	1.68 ± 0.24	1.95 ± 0.39	.004
Aortic arch	1.67 ± 0.28	1.85 ± 0.38	.025
Ascending aorta	1.70 ± 0.29	1.88 ± 0.37	.028
Descending aorta	1.73 ± 0.28	1.90 ± 0.31	.028
Suprarenal abdominal aorta	1.72 ± 0.23	1.83 ± 0.38	.185
Infrarenal abdominal aorta	1.67 ± 0.27	1.87 ± 0.38	.012

Data are expressed as mean ± standard deviation, except where stated otherwise.
HDL, High-density lipoprotein; *LDL*, low-density lipoprotein; *NA*, not applicable; *PASI*, Psoriasis Area and Severity Index; *PET/CT*; positron emission tomography—computed tomography.

Table II. Clinical characteristics of 10 study participants who achieved PASI75 after treatment

Characteristic	Before treatment, N = 10	After treatment, N = 10	*P* value
Age, years	41.6 ± 6.5		NA
Sex, male, % (n)	60 (6)		NA
Body mass index, kg/m^2	24.6 ± 6.1		NA
% Body surface area involved	34.1 ± 12.6	5.1 ± 4.8	
PASI	14.2 ± 9.5	3.1 ± 3.4	
Total cholesterol, mg/dL	202.75 ± 52.83	-	
LDL cholesterol, mg/dL	115.17 ± 50.21	-	
Triglycerides, mg/dL	125.83 ± 90.59	-	
HDL cholesterol, mg/dL	53.67 ± 10.13	-	
C-reactive protein, mg/dL	0.21 ± 0.27	-	
Leucocytes, $10^3/\mu$L	6.83 ± 1.82	-	
Neutrophils, $10^3/\mu$L	60.58 ± 8.19	-	
Lymphocytes, %	30.49 ± 7.09	-	
Monocytes, %	5.52 ± 1.32	-	
Baseline PET/CT values			
Liver	2.40 ± 0.65	1.85 ± 0.55	.0045
Spleen	1.97 ± 0.50	1.58 ± 0.32	.0045
Aortic arch	1.89 ± 0.52	1.50 ± 0.29	.0201
Ascending aorta	1.95 ± 0.46	1.46 ± 0.36	.0071
Descending aorta	1.92 ± 0.31	1.57 ± 0.25	.0121
Suprarenal abdominal aorta	1.85 ± 0.41	1.53 ± 0.23	.0710
Infrarenal abdominal aorta	1.89 ± 0.43	1.49 ± 0.33	.0040

Data are expressed as mean ± standard deviation, except where stated otherwise.
HDL, High-density lipoprotein; *LDL*, low-density lipoprotein; *NA*, not applicable; *PASI*, Psoriasis Area and Severity Index; *PET/CT*; positron emission tomography—computed tomography; -, not done.

aorta (ascending thoracic aorta, aortic arch, descending thoracic aorta, suprarenal abdominal aorta, and infrarenal abdominal aorta). By using the CT images for coregistration, areas of interest were identified on the PET images. The ^{18}F-FDG uptake was quantified by drawing a region of interest around the liver, spleen, and each part of the aorta on every slice of the coregistered ^{18}F-FDG PET/CT images. The maximal arterial standardized uptake value was then calculated as the maximal pixel activity within the region of interest of every slice. The maximum standardized uptake values were measured along the liver, spleen, and 5 parts of the aorta at ~5-mm intervals in the axial orientation. The standardized uptake value is a widely used method for quantification of ^{18}F-FDG PET/CT data.

Statistical analyses

The 2 groups (psoriasis vs healthy) were compared by using a *t* test for normally distributed continuous variables and the Wilcoxon rank sum test for nonnormal distributions. To assess changes within each group, a paired *t* test was performed. For comparison between the groups of dichotomous variables, Fisher's exact test was used with cell numbers <5; otherwise, the χ^2 test was used. Two-tailed probability values are reported, and statistical significance was assumed when the *P* value was <.05. Descriptive data are presented as mean ± SD for continuous parametric variables. Linear regression was performed, adjusted for sex, age, and body mass index (BMI); thus, we could investigate the significance of the differences between the 2 groups even after accounting for the effects of the aforementioned characteristics. All the statistical analyses were performed with SAS JMP (SAS Institute, Cary, NC).

RESULTS

Patients' characteristics

During March 2013-February 2015, a total of 25 patients and 47 healthy individuals were referred and screened for the study. The baseline clinical characteristics of the study participants are listed in Table I.

The basic demographic profiles did not differ significantly between the patients with psoriasis and the healthy controls ($P > .05$). The patients with

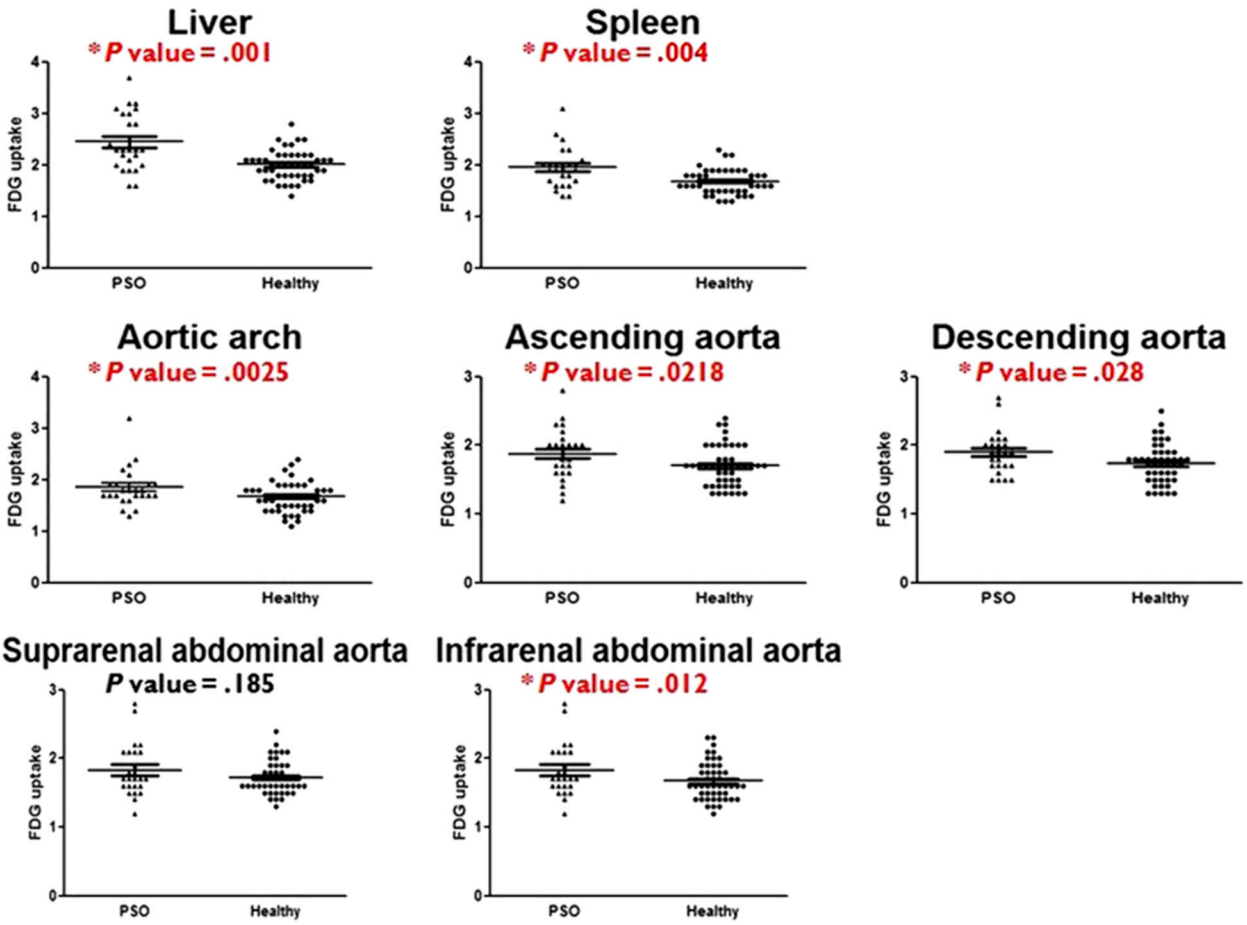

Fig 2. Comparison of ^{18}F-FDG uptake between the psoriasis and healthy groups. The ^{18}F-FDG uptake in the psoriasis group (n = 25) and healthy controls (n = 47) is shown. ^{18}F-FDG PET/CT imaging showed increased ^{18}F-FDG uptake in the liver, spleen, and 4 parts of the aorta in patients with psoriasis compared with controls. Bars indicate the mean ± SD values. *Statistically significant ($P < .05$). *^{18}F-FDG PET/CT*, ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography.

psoriasis had the disease for a mean duration of 13.5 (range 2-32) years and a mean BSA of 32.9% and a mean PASI of 13.1.

Of the 25 patients screened for enrollment, 10 with moderate-to-severe psoriasis were assigned to a treatment group to receive ustekinumab. The disease duration in these patients ranged 7 months-26 years, with a mean of 15.0 years. The mean PASI was 14.2, and the mean BSA involved was 34.1%, with the minimally affected BSA being 14.0%. All the patients who started receiving ustekinumab achieved PASI75, and the mean number of ustekinumab injections to achieve PASI75 was 3.2. The clinical characteristics of the 10 participants who received ustekinumab are listed in Table II.

Comparisons of ^{18}F-FDG PET/CT findings between psoriasis and healthy groups

^{18}F-FDG PET/CT imaging revealed greater increases in ^{18}F-FDG uptake in the liver, spleen, and 4 parts of the aorta in the psoriasis group than in the control group ($P < .05$; Fig 2).

Comparison of ^{18}F-FDG PET/CT findings among patients with psoriasis

In the psoriasis group, the patients with moderate-to-severe psoriasis (PASI >10) had more significant increases in ^{18}F-FDG uptake in the liver, spleen, and all parts of the aorta than the patients with mild psoriasis (PASI ≤10; Fig 3, *A*). However, data on ^{18}F-FDG uptake showed no significant

difference between the psoriasis group with a BSA of >10 and those with a BSA of ≤10. The obese patients with psoriasis (BMI >25 kg/m^2) showed increased ^{18}F-FDG uptake in the liver, spleen, and all parts of the aorta compared with the normal weight psoriasis group (BMI ≤25 kg/m^2; Fig 3, *B*). No significant difference in the psoriasis group was found between patients aged >40 years and those aged ≤40 years.

Comparison of ^{18}F-FDG PET/CT findings before and after treatment with ustekinumab

After PASI75 was achieved, the mean PASI was reduced from 17.7 to 1.2, showing a 93.2% improvement. With respect to systemic and vascular inflammation, ^{18}F-FDG uptake was reduced in the liver, spleen, and all parts of the aorta ($P < .05$), as shown in Fig 4. The results were the same after the multivariate analysis adjusting for risk factors of age, sex, and BMI ($P < .05$). Ustekinumab-associated changes on the ^{18}F-FDG PET/CT scans are shown in Fig 5, *A-C*.

DISCUSSION

Psoriasis is regarded as an immune-mediated inflammatory disease associated with a high risk for systemic comorbidities, such as cardiovascular disease (CVD) and metabolic syndrome.[13] Our findings showed that patients with psoriasis had increased hepatic, splenic, and arterial inflammation compared with the matched control group. In addition, we showed that inflammation of the liver, spleen, and arteries was greater in the severe and obese psoriasis groups. These findings highlight the need for improved characterization of metabolic syndrome and CVD risk in patients with psoriasis, especially those who are obese or have severe psoriasis. We also showed that ustekinumab dramatically reduced inflammation of the liver, spleen, and arteries, suggesting that systemic therapy might reduce not only inflammation of the skin but also that of the liver, spleen, and vessels. The results of this study on psoriasis are likely to be relevant to other systemic therapies that achieve the goal of PASI75. These data suggest further study of early intervention strategies for achieving PASI75 to prevent metabolic syndrome and cardiovascular events in patients with psoriasis.[17]

Previous studies described increased arterial inflammation in patients with psoriasis, which diminished with adalimumab administration.[18] Another study showed that mild psoriasis is associated with a higher risk for subclinical arterial and hepatic inflammations.[16] We showed increased inflammatory activities in the liver, spleen, and arteries in patients with psoriasis, especially in the severe and obese groups. Moreover, we report that hepatic, splenic, and arterial inflammations were significantly reduced after PASI75 was achieved with ustekinumab treatment. Increased arterial ^{18}F-FDG uptake has been shown to predict future CVD events, which suggests that the increased risk for CVD in the setting of psoriasis is reduced with ustekinumab administration.[19]

We also evaluated the correlations between inflammatory and lipid measurements and ^{18}F-FDG uptake in the liver, spleen, and arteries. Baseline C-reactive protein level did not predict inflammation of the liver, spleen, and arteries. However, baseline low-density lipoprotein cholesterol level had concomitant correlations with inflammation of the liver, spleen, and arteries, and eosinophils correlated with that of the arteries. No significant change in low-density lipoprotein cholesterol level or eosinophil count was observed after PASI75 was achieved with ustekinumab therapy. A previous study reported that short-term use of ustekinumab had no positive or negative effect on CVD; however, ustekinumab reduced cardiovascular inflammation for up to 4 years.[20] Our study showed that a mean of 5 months of ustekinumab therapy (mean 3.2 injections) decreased not only vascular inflammation but also hepatic and splenic inflammation. Further study is needed to determine any change in low-density lipoprotein cholesterol level with long-term use of ustekinumab therapy.

Several limitations of this study need to be addressed. First, we provided short-term treatment, but CVD and metabolic syndrome develop over a period of several years. However, in previous studies, sustained effects were found at 18 months, and hepatic, splenic, and arterial inflammation can be expected to follow this course.[21,22] Second, our study does not provide outcome data concerning cardiovascular events or metabolic syndrome and only shows surrogate markers in a limited (Korean) population, and broader exploration is warranted. However, ^{18}F-FDG uptake seems to be of prognostic value in assessing CVD and metabolic syndrome and can therefore be a valuable biomarker in diseases with relatively low numbers of patients.

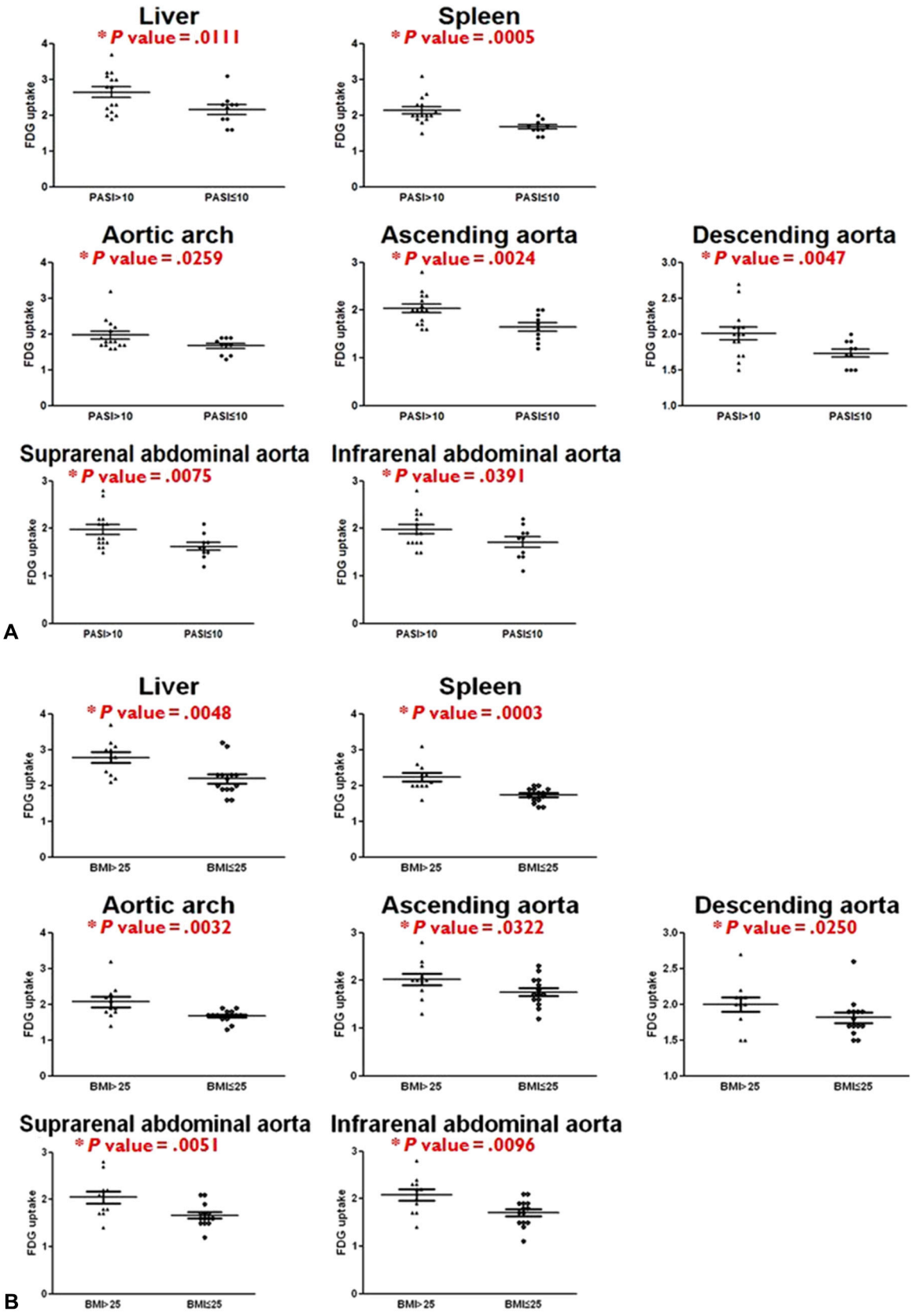

Fig 3. Comparison of ^{18}F-FDG uptake among patients in the psoriasis group. **A**, Comparison of ^{18}F-FDG uptake among patients in the psoriasis group by PASI score. Patients with moderate-to-

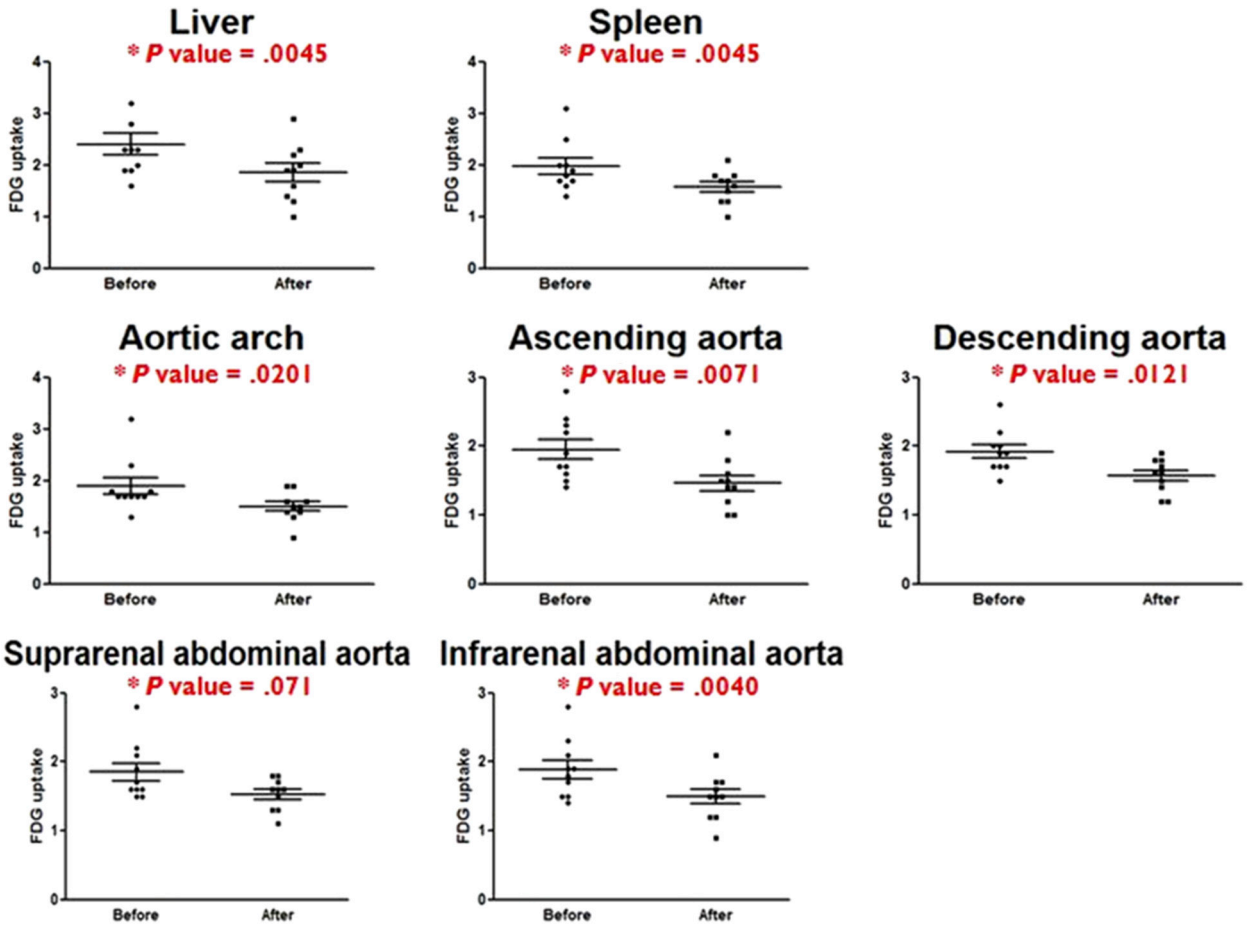

Fig 4. Comparison of ^{18}F-FDG uptake before and after treatment with ustekinumab. Changes in ^{18}F-FDG uptake on PET/CT imaging of the liver, spleen, and arteries after PASI75 was achieved with ustekinumab therapy (n = 25). ^{18}F-FDG uptake was reduced in the liver, spleen, and all parts of the aorta after ustekinumab therapy. Bars indicate the mean ± SD values. *Statistically significant ($P < .05$). *^{18}F-FDG*, ^{18}F-fluorodeoxyglucose; *PASI75*, 75% improvement from baseline Psoriasis Area and Severity Index score; *PET/CT*, positron emission tomography–computed tomography.

We showed that the patients with psoriasis had increased hepatic, splenic, and arterial inflammation, especially in the severe and obese groups, which decreased after PASI75 was achieved with ustekinumab therapy. Cardiovascular risk screening and management are recommended for patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis by The European League Against Rheumatism.[23] Our results support that similar recommendations are needed for patients with psoriasis, especially those in the severe and obese groups, as the inflammation levels in their liver, spleen, and arteries were elevated.

severe psoriasis (PASI >10) (n = 15) had significantly increased ^{18}F-FDG uptake in the liver, spleen, and all parts of the aorta compared with patients with mild psoriasis (PASI ≤10) (n = 10). **B**, Comparison of ^{18}F-FDG uptake among patients in the psoriasis group by BMI. The patients with psoriasis who were obese (BMI >25 kg/m^2) (n = 11) showed increased ^{18}F-FDG uptake in the liver, spleen, and all parts of the aorta compared with patients with psoriasis who had a normal weight (BMI ≤25 kg/m^2) (n = 14). Bars indicate the mean ± SD values. *Statistically significant ($P < .05$). *BMI*, Body mass index; *^{18}F-FDG PET/CT*, ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography; *PASI*, Psoriasis Area and Severity Index.

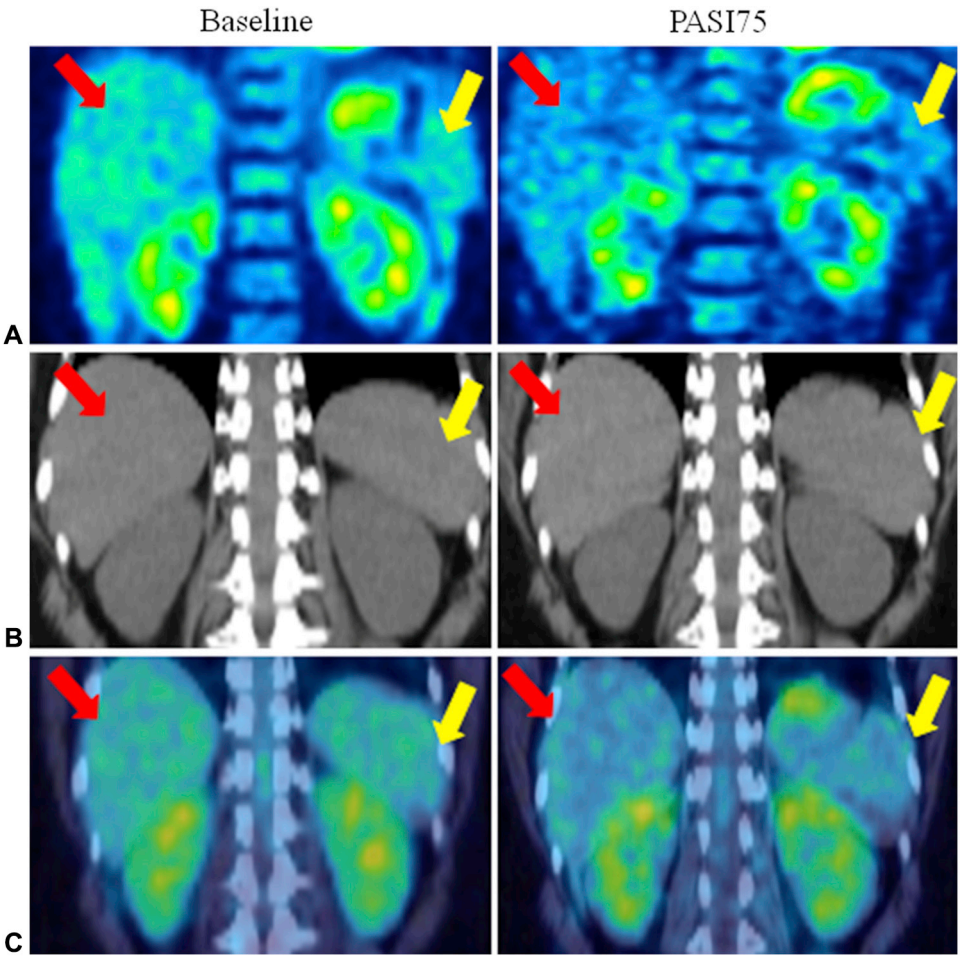

Fig 5. Ustekinumab-associated changes on the ^{18}F-FDG PET/CT scans. ^{18}F-FDG uptake in the liver (*red arrow*) and spleen (*yellow arrow*) was decreased after PASI75 was achieved with ustekinumab treatment: PET (**A**), CT (**B**), and PET/CT fusion (**C**). *^{18}F-FDG PET/CT*, ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography; *PASI75*, 75% improvement from baseline Psoriasis Area and Severity Index score.

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